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DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF DEAFNESS

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It is impossible to discuss within the allotted time all phases of the subject assigned to me, and the following facts about the diagnosis of middle and inner ear deafness are presented because I know they are accurate and think they will be of value in the interpretation of hearing tests.

There are three common types of impairment of hearing: the type due to a lesion of the conduction apparatus which interferes with the transmission of sound to the cochlea; that due to a lesion in Corti's organ or the cochlear nerve which interferes with the perception of sound, and a combined conduction and perception deafness. It is possible to have impaired hearing due to a nuclear or auditory pathway lesion, but this is rare and when it occurs the patient always has symptoms of intracranial tumor or of a degenerative process in the central nervous system. Probably more than 98 per cent of all deafness is due to a lesion in the middle or inner ear or in the cochlear nerve. Observations made in the Otological Research Laboratory of Johns Hopkins University [1] in 1928 on patients with an infiltrating glioma show that after the cochlear nerves enter the brain stem their bilateral representation is so complete that the entire right temporal lobe or indeed the entire right cerebral hemisphere may be removed without impairing the hearing in either ear. To cause deafness a tumor of the brain or other type of central lesion must be extensive enough to involve the auditory pathway on both sides. This of course is not true when the cochlear nerve within the temporal bone or in the cerebellopontile angle is affected.

Before discussing the diagnosis of the different types of impaired hearing I wish to call attention to changes in hearing brought about by

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From the Otological Research Laboratory of the Johns Hopkins University.

Read at the Forty-Fourth Annual Meeting of the American Laryngological, Rhinological and Otological Society, Atlantic City, N. J., April 28, 1938.

1. Bunch, C. C.: Auditory Acuity After Removal of the Entire Right Cerebral Hemisphere, J. A. M. A. **90**:2102 (June 30) 1928.

age.[2] The chart in figure 1 is an average of the audiograms of 693 patients with normal hearing for their age. With each decade the hearing for the high frequencies becomes more and more impaired. It is essential to know this when interpreting an audiometer chart.

Many abnormal conditions in the middle ear cause no impairment of hearing, such as a tympanic membrane retracted and adherent to the promontory and fibrous or myxomatous tissue in the niche of the round window, as illustrated in figure 2. Every otologist has seen dry perforations, scars or deposits of calcium in the tympanic membrane that do not impair hearing.

The three conditions in the middle ear that do impair hearing are: partial or total obstruction of the eustachian tube; any lesion that interferes with the movement of the ossicles, and fixation of the footplate of the stapes due to otosclerosis.

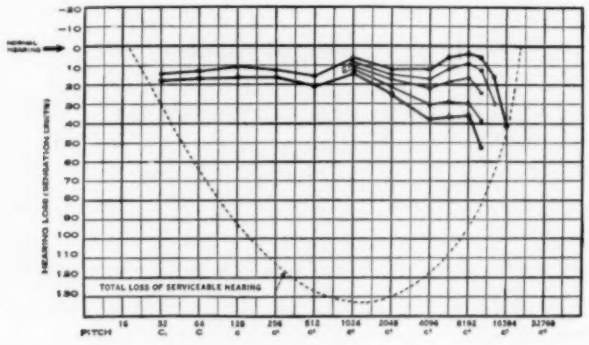

Fig. 1.—An average of the audiograms of 693 patients with normal hearing for their age (Bunch and Raiford's chart 10 transferred to a standard audiograph form). With advancing age there is little change in the ability to hear 1024 double vibrations and all lower tones; with each decade above the age of 20 there is increasing impairment for the higher frequencies.

For diagnostic purposes and for the prevention of a common type of deafness in early adult life it is important to know that during the early stages of obstruction of the eustachian tube in children the hearing is more impaired for high than for low tones (fig. 3).[3] The cause for obstruction of the eustachian tube in childhood is an overgrowth of lymphoid tissue around its pharyngeal orifice, a hypersecretion of mucus

2. Bunch, C. C., and Raiford, T. S.: Race and Sex Variations in Auditory Acuity, Arch. Otolaryng. **13**:423-434 (March) 1931. Ciocco, A. A.: Observations on the Hearing of 1,980 Individuals: A Biometric Study, Laryngoscope **42**:837-856 (Nov.) 1932.

3. Crowe, S. J., and Guild, S. R.: Impaired Hearing for High Tones, Acta oto-laryng. **26**:138-142, 1938.

in the tube or a chronic suppuration in one or more of the peritubal cells without clinical evidence of otitis media. A child suffering from one of these conditions is fortunate to have acute otitis media which

Fig. 2.—The tympanic membrane is adherent to the promontory and the round window niche is filled with myxomatous tissue. The ossicular chain and cochlea are normal. The hearing of this patient, aged 17, was normal.

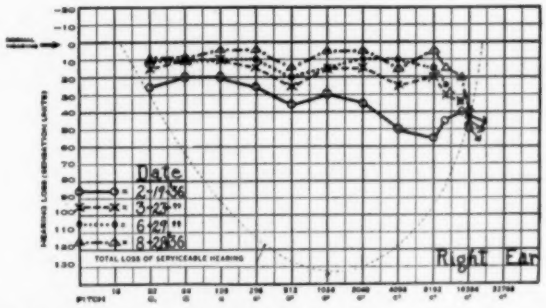

Fig. 3.—Impaired hearing, greater for high tones (solid line), and the improvement that followed radium treatment of lymphoid tissue in and around the pharyngeal orifice of the eustachian tube.

directs attention to his ears. Deafness, which may not appear until much later in life, should always be thought of when a child has fre-

quent colds, chronic nasal obstruction and hypertrophied lymphoid tissue on the lateral and posterior pharyngeal walls. In addition to the removal of tonsils and adenoids and treatment or operation for nasal obstruction or sinus infection, these patients should be followed and reexamined from time to time to be sure their eustachian tubes are clear and the hearing for the higher frequencies is normal. If the impaired hearing fails to clear up and symptoms of tubal catarrh continue, treatment of the persistent lymphoid tissue with radium or roentgen rays is indicated. The overgrowth of lymphoid tissue around the orifice of the eustachian

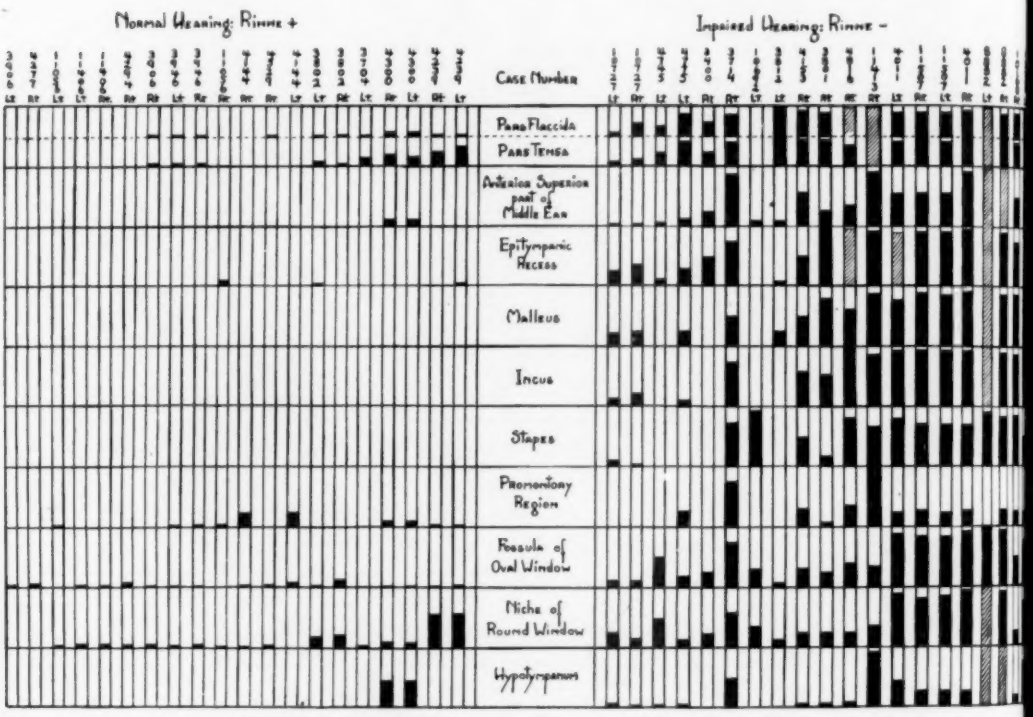

Fig. 4.—A chart showing in black the location and extent of the pathologic lesion in the middle ear for 20 patients with normal hearing and 20 with conduction deafness. It is striking that no patient with normal hearing had a lesion of the malleus, incus or stapes.

tube cannot be diagnosed in children by palpation of the nasopharynx or inspection with a mirror. A nasopharyngoscope must be used, and if necessary the child is given avertin with amylene hydrate or some similar anesthetic to insure a good view. If the condition is not recognized and properly treated in its incipiency, the impairment of hearing progresses from one octave to another toward the low end of the scale, and finally, when the hearing for tones between 2000 and 4000 double

vibrations becomes involved, the patient begins to be noticeably deaf. At this stage, which may not be reached for ten years or more, the damage in the middle ear is often permanent and treatments by roentgen irradiation, inflation, tubal applications and dilations are of no avail.

The correlations between functional test and histologic study [4] given in figures 4, 5, 6 and 7 show that any lesion which interferes with movement of the ossicles causes a marked loss of hearing. In the

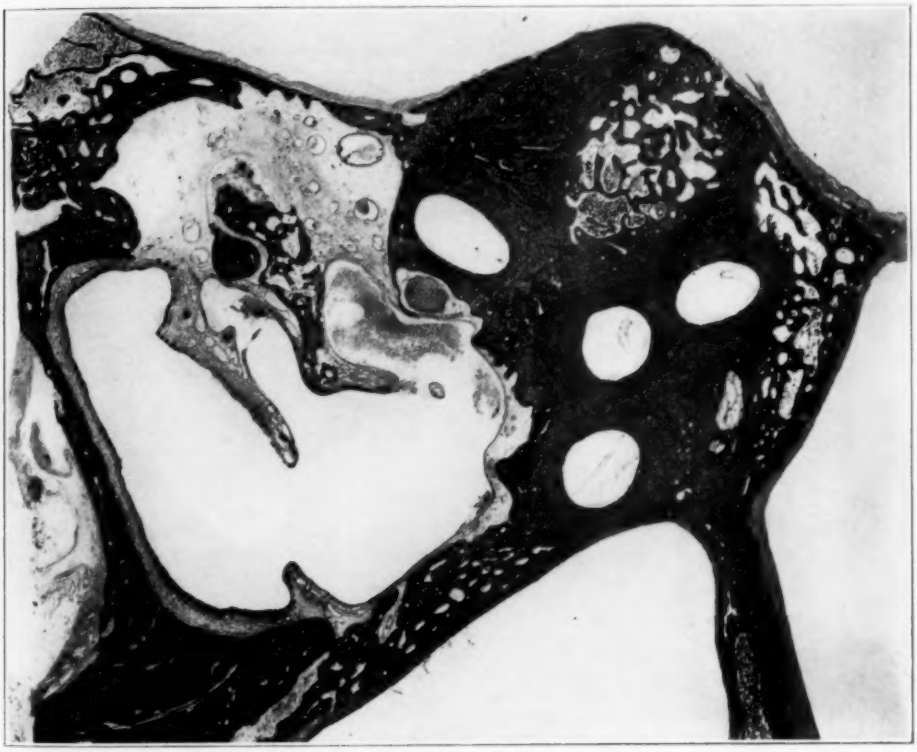

Fig. 5.—Conduction deafness due to chronic suppuration in the middle ear. There is a defect in the tympanic membrane, and the head of the malleus and the incus are embedded in fibrous tissue. The stapes is relatively free and the cochlea normal.

presence of obstruction of the eustachian tube or of a lesion which interferes with the movement of the malleus and incus, the impairment of hearing usually begins with the higher frequencies, while in the presence of otosclerosis involving the stapes alone the low as well as

4. Polvogt, L. M., and Bordley, J. E.: Pathologic Changes in the Middle Ear of Patients with Normal Hearing and of Patients with a Conduction Type of Deafness, Ann. Otol., Rhin. & Laryng. **45**:760-768 (Sept.) 1936.

the high tones are impaired. This is illustrated by the audiogram and photograph of the stapes in figure 8. In the case of ankylosis of the stapes illustrated here, histologic study of the cochlea shows no lesion of the nerve or its end organ, and the round window membrane is normal. The inference is that high frequencies are not transmitted to the cochlea through the round window membrane.

In addition to changes due to age and conditions in the middle ear, the early stages of involvement of the inner ear or of the cochlear nerve may cause a selective loss of hearing for high tones. I shall give

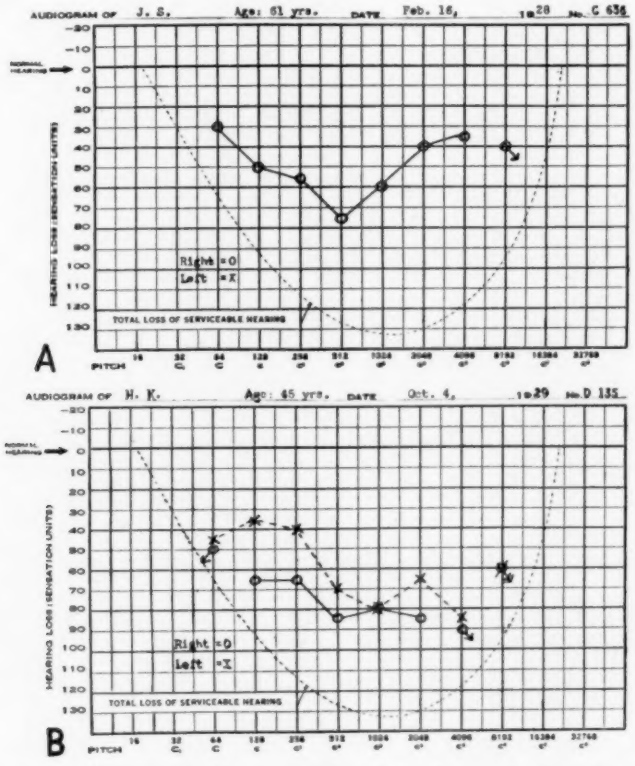
AUDIOGRAM OF J. S. Age: 61 yrs. DATE Feb. 16, 1928 No. C 636
HEARING LOSS (SENSATION UNITS)
Right = O
Left = X
TOTAL LOSS OF SERVICEABLE HEARING
PITCH
A
AUDIOGRAM OF H. K. Age: 65 yrs. DATE Oct. 4, 1929 No. D 135
HEARING LOSS (SENSATION UNITS)
Right = O
Left = X
TOTAL LOSS OF SERVICEABLE HEARING
PITCH
B

Fig. 6.—*A*, audiogram of the ear pictured in figure 5. Impairment in the middle of the speech range is greater than for the lower and higher tones. *B*, audiogram of the ear pictured in figure 7. The hearing is impaired more for high than for low tones, and no tone above 4096 is heard.

three examples: 1. An acoustic tumor (fig. 9) which originates in the vestibular nerve but is not large enough to compress either blood vessels or nerves against the bony walls of the internal meatus causes no symptoms of any kind.[5] As it grows the patient begins to have occipital

5. Hardy, M., and Crowe, S. J.: Early Asymptomatic Acoustic Tumor: Report of Six Cases, Arch. Surg. **32**:292-301 (Feb.) 1936.

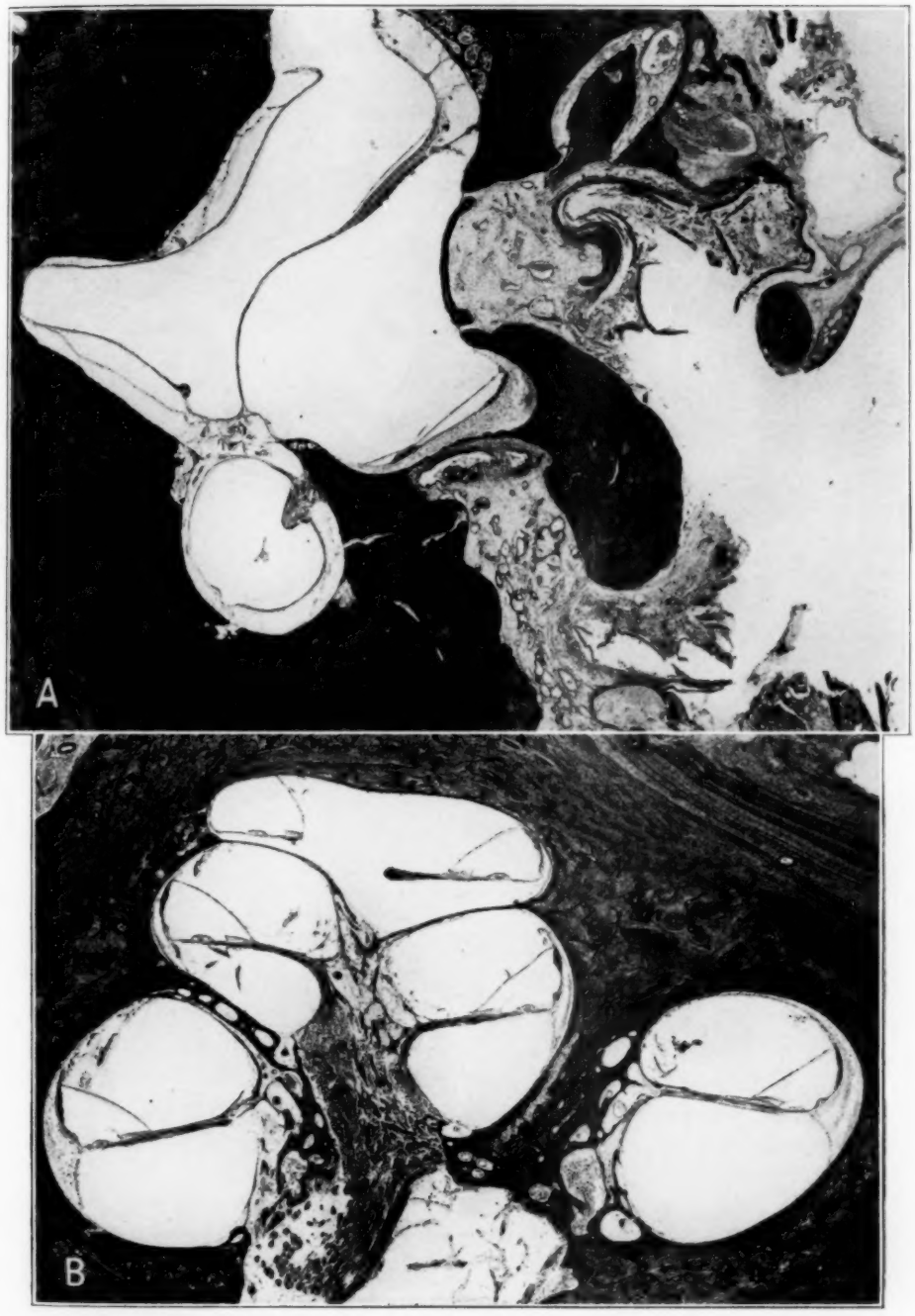

Fig. 7.—*A*, entire stapes embedded in scar tissue and round window niche filled. *B*, normal nerve and Corti's organ in all turns of the cochlea. This case illustrates how much impairment can result from pure middle ear lesions.

headache, ataxia and, what concerns otologists, impaired hearing for high tones, as shown in figure 10. As the tumor increases in size, the deafness progresses by involving the lower tones until the audiogram becomes a straight line, and the final stage is total deafness. When involvement of the fifth nerve, choked disk and other signs and symptoms are diagnostic of an advanced acoustic tumor, the otologist

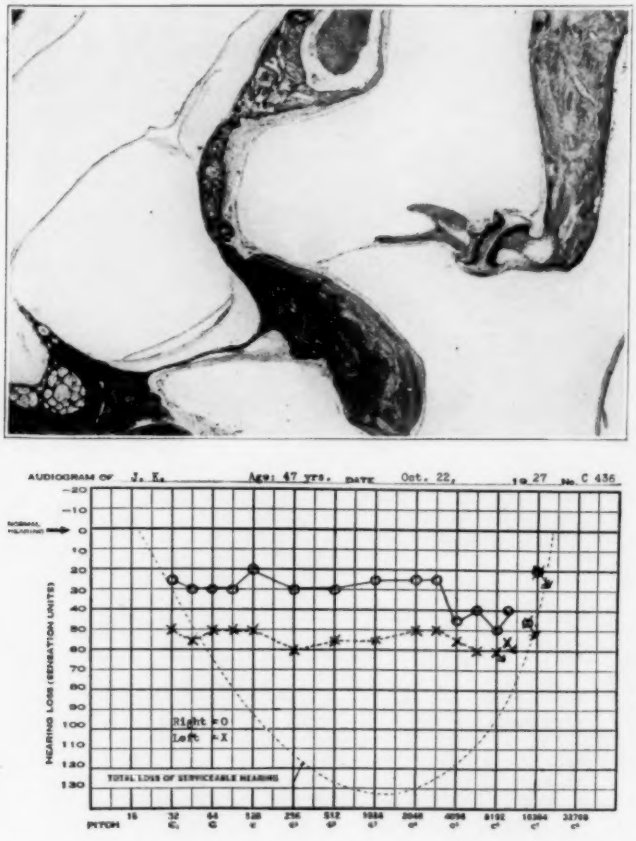
AUDIOGRAM OF J. K. Age: 47 yrs. DATE Oct. 22, 1927 No. C 436
HEARING LOSS (DEVIATION UNITES)
PITCH
Right = O
Left = X
TOTAL LOSS OF SERVICEABLE HEARING

Fig. 8.—Ankylosis of the footplate of the stapes of the left ear, due to otosclerosis. Other parts of the middle ear and the ossicular chain are normal. Audiogram of the same ear, showing an equal impairment for high and for low tones.

may draw a false conclusion from audiometer and tuning fork tests if he fails to use masking, as illustrated in figure 11. The audiometer test of the patient concerned showed impaired hearing for 4096 double vibrations and the two highest tones on the right, and on the left a moderate impairment for all tones except those above 4096, which are not heard. When the test is repeated with the good ear masked, it

shows total deafness on the left. 2. Ménière's disease [6] causes progressive deafness, as shown in figure 12. The patient whose audiograms are shown was having vertigo, tinnitus and some difficulty in hearing in the right ear in November 1934; as the disease progressed

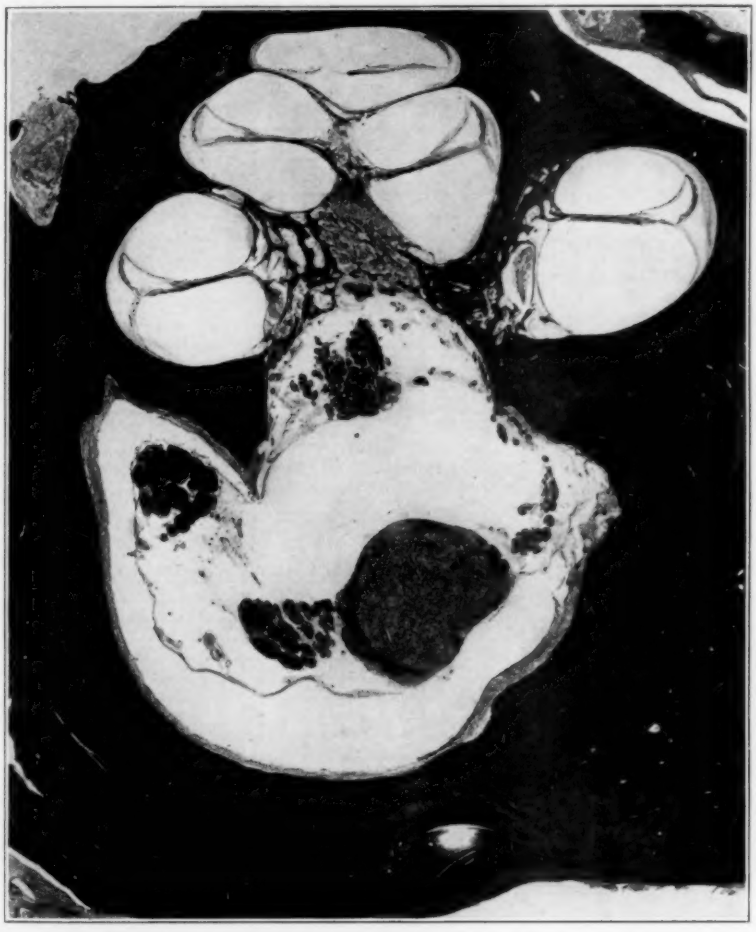

Fig. 9.—Asymptomatic acoustic tumor arising in the vestibular nerve, accidentally discovered. As a tumor in this location increases in size it compresses the nerves and blood vessels against the bony walls of the internal meatus, and the first auditory symptom is impaired hearing for high tones.

the hearing for low tones became more and more impaired, as shown by the tests made in January 1935 and April 1937. 3. When patients

6. Crowe, S. J.: Ménière's Disease: A Study Based on Examinations Made Before and After an Intracranial Division of the Vestibular Nerve, Medicine **17**:1-36 (Feb.) 1938.

with Ménière's disease are treated by intracranial division of the vestibular nerve, some of the cochlear nerve is occasionally divided, since the two nerves are so closely bound together. The invariable result of such an accident is a total loss of hearing for one or more octaves in the high end of the scale. This is clearly shown in figure 13. The entire vestibular nerve and all but a few fibers of the left cochlear

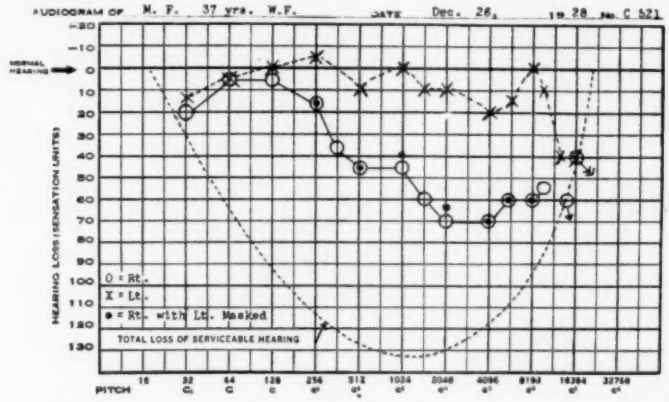
AUDIOGRAM OF M. F. 37 yrs. W.F. DATE Dec. 26, 19 28 No. C 521
NORMAL HEARING
HEARING LOSS (SENSATION UNITS)
O = Rt.
X = Lt.
● = Rt. with Lt. Masked
TOTAL LOSS OF SERVICEABLE HEARING
PITCH

Fig. 10. Hearing good for low tones but impaired for high tones owing to an acoustic tumor on the right, which was larger than the one shown in figure 9.

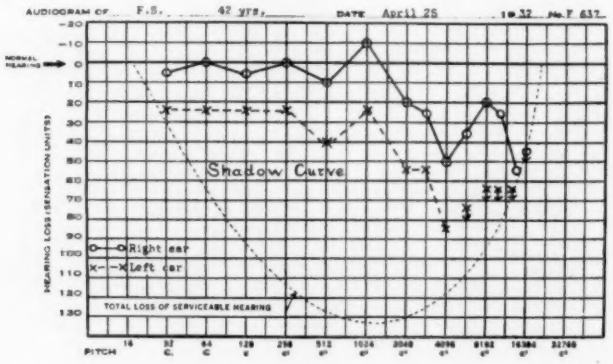
AUDIOGRAM OF F.S. 42 yrs. DATE April 25 19 32 No. F 637
NORMAL HEARING
HEARING LOSS (SENSATION UNITS)
Shadow Curve
O—O Right ear
X—X Left ear
TOTAL LOSS OF SERVICEABLE HEARING
PITCH

Fig. 11.—Audiogram of a patient with a large tumor of the cerebellopontile angle on the left. The audiogram of the left ear is false; when the right was masked, total deafness on the left was demonstrated.

nerve were divided. Before operation the patient heard all tones up to 8192 double vibrations; when tested a year later she failed to hear anything above 256, but for 128 and lower tones there was little change. This observation suggests either that transmission of the higher frequencies to the brain requires a large number of nerve fibers or that

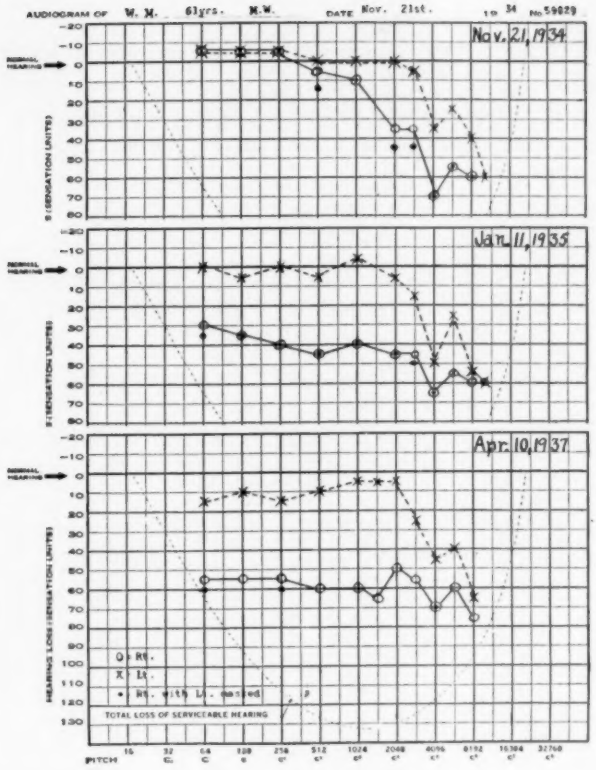

Fig. 12.—A series of audiograms of a patient with Ménière's disease. The first auditory symptom was tinnitus and impaired hearing for high tones; as the deafness progressed the hearing for low tones became more and more impaired.

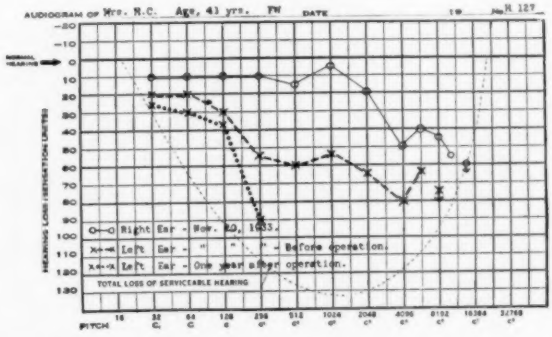

Fig. 13.—The first auditory symptom of an acoustic tumor is impaired hearing for high tones (fig. 10). As more fibers of the cochlear nerve are pressed on by the growing tumor the hearing for lower tones is affected. A similar type of hearing impairment results when some of the cochlear nerve is accidentally divided at operation for Ménière's disease (fig. 12). When a few cochlear fibers are cut only one or two octaves at the high end of the scale are lost, but when most of the nerve is cut four and a half octaves are lost. This audiogram shows the hearing for 256 double vibrations also to be much impaired.

there is localization in Corti's organ for high tones only and low tones are transmitted by any undamaged nerve fibers that remain, without regard to the location of their end organ in the cochlea.

Other studies on inner ear deafness made in this laboratory [7] showed conclusively the localization in the cochlea for 2048 double vibrations

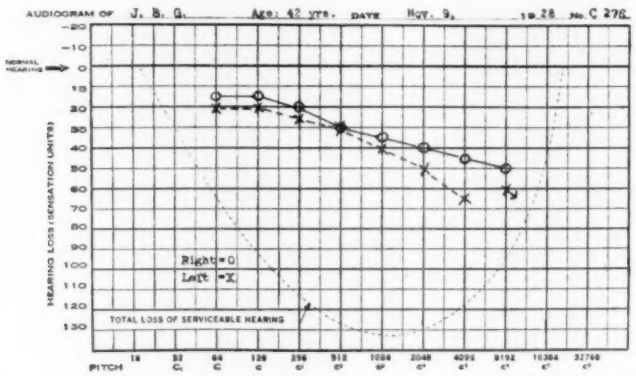
AUDIOGRAM OF J. B. G. Age: 42 yrs. DATE Nov. 9, 1928 No. C 276
NORMAL HEARING
HEARING LOSS (SENSATION UNITS)
Right = O
Left = X
TOTAL LOSS OF SERVICEABLE HEARING
PITCH

Fig. 14.—When there is no clinical evidence of conduction deafness and the audiogram shows good hearing for low tones but increasing impairment for each octave toward the high end of the scale, the lesion is an atrophy of the nerve supplying the basal turn of the cochlea. The cause is unknown.

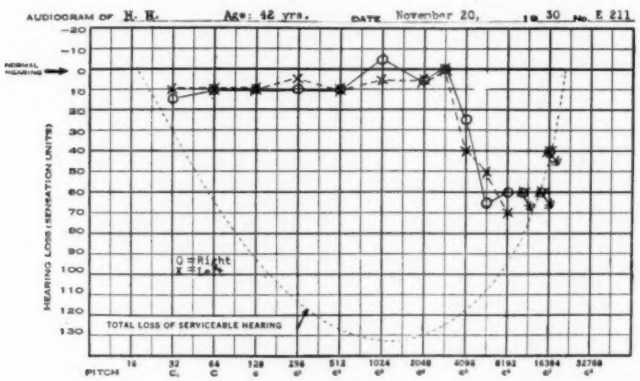
AUDIOGRAM OF H. H. Age: 42 yrs. DATE November 20, 1930 No. E 211
NORMAL HEARING
HEARING LOSS (SENSATION UNITS)
O = Right
X = Left
TOTAL LOSS OF SERVICEABLE HEARING
PITCH

Fig. 15.—When the middle ear and the tube are normal and the hearing is good for all tones below 2000 or 3000 double vibrations, but is markedly impaired for all higher tones, the lesion is an atrophy of both nerve and Corti's organ in the basal coil. The cause is not known.

and higher frequencies, but no evidence was found for localization of tones below 2048. Two points of practical importance in the differ-

7. Crowe, S. J.; Guild, S. R., and Polvogt, L. M.: Observations on the Pathology of High-Tone Deafness, Bull. Johns Hopkins Hosp. **54**:315-379 (May) 1934.

ential diagnosis of deafness resulted from this study.[7] When the eustachian tube and the middle ear are normal and the audiogram shows good hearing for low tones but an impairment which begins at 256 or 512 and increases gradually with each octave toward the high end of the scale, as illustrated in figure 14, the lesion is an atrophy of the cochlear nerve supplying the basal turn of the cochlea. The organ of Corti is not affected, and the nerve to the upper middle and apical coils is normal. When the eustachian tube and middle ear are normal and the audiogram shows an abrupt or sharply localized impairment for high tones, as in figure 15, both the nerve and the organ of Corti in the basal coil are atrophic. The cause is unknown, but the location and type of lesion are known. Intensive study of patients with these types of hearing defect is the only way to add to knowledge of their causes; no information on this subject has come from animal experiments.

Audiometers, tuning forks and masking were discussed in the report of the committee on hearing tests of the American Otological Society.[8]

In conclusion I wish to emphasize the fact that a differential diagnosis of the various types of deafness cannot be made with tuning fork or audiometer tests alone. To be of any value an audiometer test must always be supplemented with fork tests. The only way to make a satisfactory differential diagnosis is to take a detailed history, to examine the upper air passages, the tympanic membranes and the eustachian tubes and to use masking when making the hearing tests. In otology as in other branches of medicine a sound knowledge of anatomy and pathology is essential for an understanding of functional disorders.

8. Report of the Committee on Methods of Testing the Hearing by Bone Conduction, Ann. Otol., Rhin. & Laryng. **45**:800 (Sept.) 1936.

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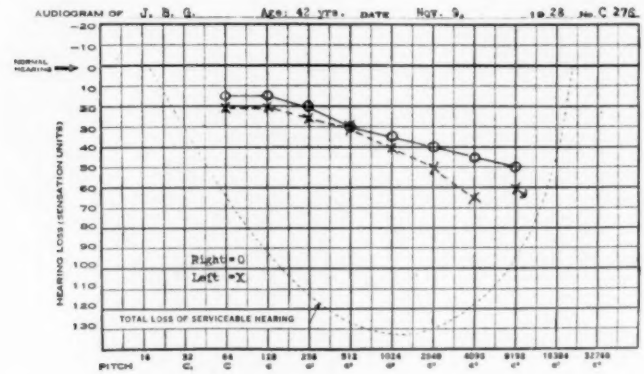
AUDIOGRAM OF J. B. G. Age: 42 yrs. DATE Nov. 9, 1928 No. C 276
NORMAL HEARING
HEARING LOSS (SENSATION UNITS)
Right = O
Left = X
TOTAL LOSS OF SERVICEABLE HEARING
PITCH

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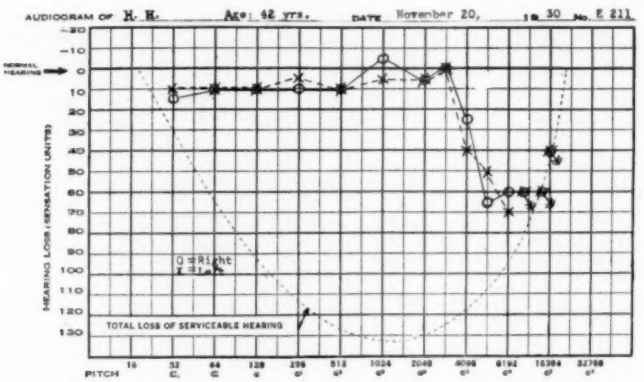
AUDIOGRAM OF H. H. Age: 42 yrs. DATE November 20, 1930 No. E 211
NORMAL HEARING
HEARING LOSS (SENSATION UNITS)
O = Right
X = Left
TOTAL LOSS OF SERVICEABLE HEARING
PITCH

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8. Report of the Committee on Methods of Testing the Hearing by Bone Conduction, Ann. Otol., Rhin. & Laryng. **45**:800 (Sept.) 1936.

STAPES, FISSULA ANTE FENESTRAM AND ASSOCIATED STRUCTURES IN MAN

I. FROM THE EMBRYO OF SEVEN WEEKS TO THAT OF TWENTY-ONE WEEKS

BARRY J. ANSON, PH.D. (MED.SC.)
JOHN E. KARABIN, M.D.
AND
JOHN MARTIN, M.D.
CHICAGO

In the course of a comprehensive study of the anatomy of the human ear, it was early realized that more precise information was needed on the development and the adult form and structure of the stapes. Not until such information became available could pathologic structure of the stapes be certainly distinguished from normal or the extent of alteration be determined. Of almost equal importance is information concerning the neighboring area—the vestibular window, fissular tracts and islands of osseous tissue of types peculiar to the temporal bone. The present paper represents the initial phase of a study of the stapedial area and includes six developmental stages between the embryo of 22.8 and that of 183 mm. crown-rump length; subsequent papers will carry the study through the stages of infant, child and adult (to the age of 70).

MATERIALS AND METHODS

For this investigation reconstructions of the stapes, together with the surrounding area, were prepared by the wax plate method.[1] Representative developmental

From the Departments of Anatomy, Otolaryngology and Surgery, Northwestern University Medical School. Contribution 267 from the Anatomical Laboratory.

Read at the meeting of the American Association of Anatomists, April 20, St. Louis, 1935. The investigation was conducted under the auspices of the Central Bureau of Research of the American Otological Society, with the general superintendence of Dr. J. Gordon Wilson.

1. The reconstructions in figures 1, 2 and 3 were prepared at a magnification of 250 diameters and the others at 125 diameters. The reconstructions of the earlier stages (22.8, 29 and 40 mm.) were prepared from the right ear and those of the advanced stages (135, 161 and 183 mm.) from the left ear. The various reconstructions include sections as follows: 22.8 mm. embryo (fig. 1), 33 sections; 29 mm. (fig. 2), 30; 40 mm. (fig. 3), 70; 135 mm. (figs. 24 and 25), 78; 161 mm. (figs. 28 and 29), 82; 183 mm. (figs. 20 and 31 to 33), 84, and 70 year (fig. 22), 86. Drawings for figures 1, 2 and 3 were prepared at the full dimensions of the reconstructions and reduced one seventh in reproduction. Drawings for figures 4,

(Footnote continued on next page)

stages were selected from the series of sections in the Harvard Embryological Collection, the collection in the department of anatomy at the University of Wisconsin and that in the department of otolaryngology at the Northwestern University Medical School.

These series were lent by Profs. F. T. Lewis, J. Lewis Bremer, T. H. Bast and J. Gordon Wilson.

Reconstructions were made of the following stages:

Embryo:	Stage	Age	Source	Series	Figures
	22.8 mm.	7½ weeks	Harvard	737	1, 4
	29 mm.	8½ weeks	Harvard	914	2, 5
	40 mm.	10 weeks	Harvard	1917	3, 6
	135 mm.	17 weeks	Wisconsin	5	7, 8, 13, 14, 24, 25
	161 mm.	19½ weeks	Wisconsin	13	9, 10, 15, 16, 28, 29
	183 mm.	21 weeks	Wisconsin	21	11,12,17-19,20-21,31-33,34-35
Adult:		70 years	Northwestern	3-3-34	22, 23

The series loaned by Professor Bast are among those on which his excellent study of ossification was based (Bast, 1930[2]).

OBSERVATIONS AND DISCUSSION

Embryo of 22.8 mm. Crown-Rump Length (7½ Weeks).—The stapes is histologically discernible as a fairly distinct mass of precartilage in the human embryo of 17.5 mm.;[3] the exact line of demarcation

5 and 6 were prepared at one-fourth and for figures 7 to 12 at one-half the full size, this bringing them to the same magnification in the plate; all were reduced three fifths in reproduction; in figures 9 and 12 the osseous tissue is indicated by stippling, and in the latter figure its limits are marked by arrows. Drawings for figures 14, 16, 18 and 19 were prepared at one-half the full size of the reconstructions and drawings for figures 13, 15 and 17 at one-fourth the size; all these were further reduced one third in reproduction. Drawings for figures 20 to 23 were prepared at one-half the size of the original reconstructions and reduced four sevenths in reproduction.

Photographs for figures 24 and 25 were taken at two-ninths the size of the original reconstruction and reproduced without reduction; those for figures 28 and 29 at two-ninths the size of the original and then reduced one sixth in reproduction; those for figures 31 to 33 at one-fifth the original size and reduced two ninths. The photomicrographs in figures 30, 34 and 35, were taken at a magnification of 31 diameters and are reproduced without reduction; those in figures 26 and 27 were reduced one fifth.

All dimensions presented in the table and the text are computed from measurements made on the reconstructions.

2. Bast, T. H.: Ossification of the Otic Capsule in Human Fetuses, Publication 121, Carnegie Institution of Washington, 1930; Contrib. Embryol. **21**:53 (June) 1930.

3. This is series 2155 in the Harvard Collection; in the numerous series of somewhat younger embryos the stapes is represented merely by a mesenchymal concentration. Likewise, in specimens from the Carnegie Collection the stapes is not clearly discernible in stages earlier than that of 18 mm. (15 mm., no. 350; 16 mm., no. 317, and 17 mm., no. 296); but it is distinguishable in the embryos of 18 mm. (no. 3609), 20 mm. (no. 128) and 21 mm. (no. 4148) as an area of condensed mesenchyme, not yet by the presence of cartilaginous matrix. At 23 mm. (no. 966) the matrix is clearly distinguishable. So far as can be judged from a study of sections, the stapes in the 25 mm. embryo (no. 4304) is similar in form to that in the 22.8 mm. stage illustrated in our figures 1 and 4.

betweeen the precartilage and the mesenchyme is, however, indefinite, the one merging by slow gradation into the other. At this stage, according to Streeter (1918),[4] the capsule, although still composed of precartilaginous tissue, is distinctly outlined.

In the embryo of 22.8 mm. the distinction is sharpened, cartilage being distinguishable from precartilage. The "stapes" is not yet stirrup shaped, but is annular; it is without definitive head, crura or base (figs. 1 and 4); these subdivisions of the future stapes are predictable only on the basis of relationship to the window and the incudal cartilage.

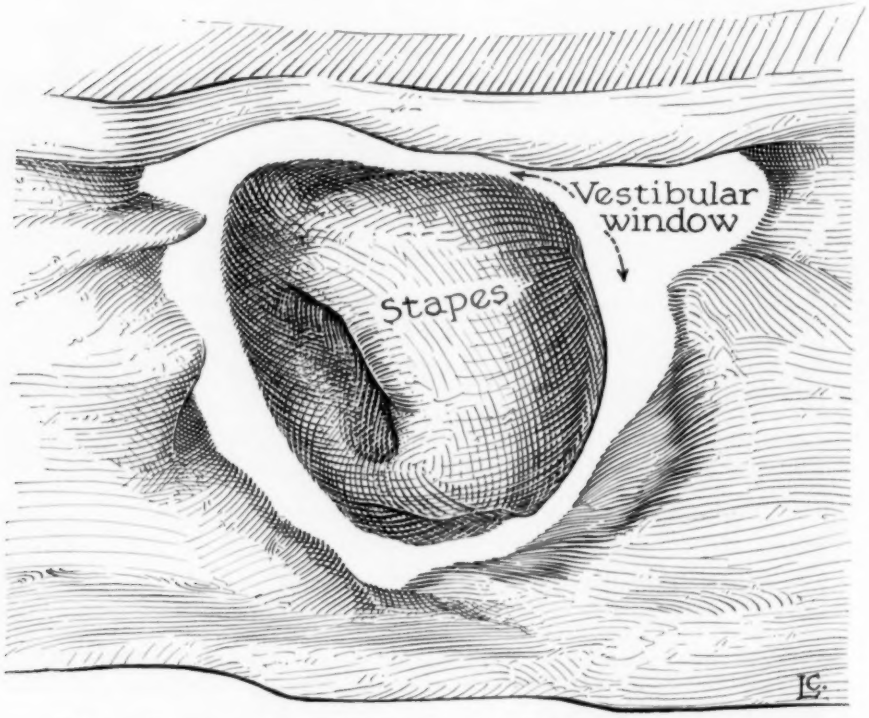


Fig. 1.—Reconstruction of the stapes and adjacent portion of the vestibular window in embryo of 22.8 mm.; × 214 (compare fig. 4).

The intercrural space is round and regular. The base of the stapes has not attained the reniform outline characteristic of the adult ossicle (fig. 1).

The length of the stapes from the base to the head is 0.294 mm.; the length of the base is 0.248 mm.; the anterior crus is 0.292 mm. long and the posterior crus 0.284 mm. The stapes is solid cartilage.

4. Streeter, G. L.: The Histogenesis and Growth of the Otic Capsule and Its Contained Periotic Tissue-Spaces in the Human Embryo, Publication 227, Carnegie Institution of Washington, 1918; Contrib. Embryol. **20**:5-54, 1918.

The outline of the vestibular window is irregular, and the space between the stapedial base and the fenestral margin is relatively wide. The labyrinthic capsule is entirely cartilaginous.

Embryo of 29 mm. Crown-Rump Length (8½ Weeks).—The form of the stapes at this stage has changed but slightly (figs. 2 and 5), but

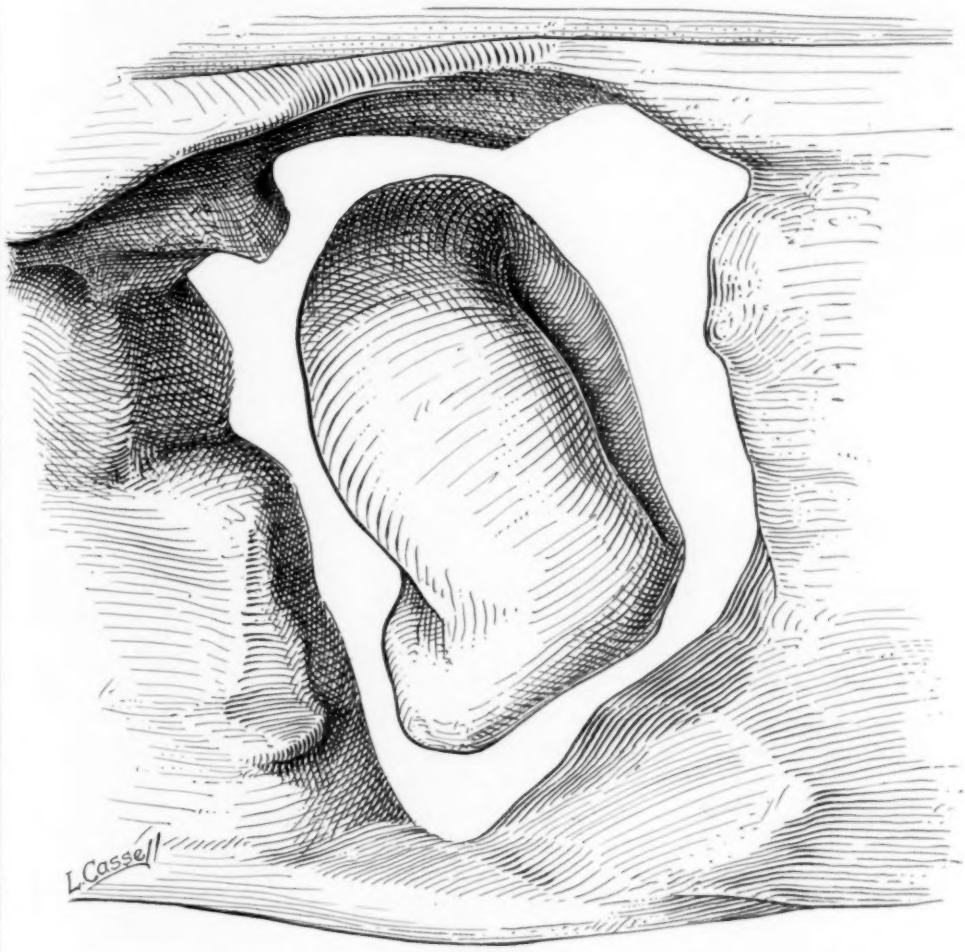


Fig. 2.—Reconstruction of the stapes and adjacent portion of the vestibular window in embryo of 29 mm.; × 214 (compare fig. 5).

its size has increased to approximately one and one-half times that of the stapedial cartilage in the 22.8 mm. embryo (table). In general the form is not yet stapedial, although the base and head are beginning to take form as thickened and somewhat flattened areas. Seen from the vestibular aspect, the base is slightly irregular, as is that of the surrounding window, owing to the rapidity of growth of cartilaginous

tissue (fig. 2). The anterior and the posterior crus are of approximately equal size (table) and similar shape and distinguishable as limbs only through their relationship to the capital and basal extremities (fig. 5). According to Broman (1898),[5] however, the stapes remains ring shaped up to the second half of the third month of embryonic life.

The otic capsule is entirely cartilaginous (Martin and Anson, 1938[6]).

Embryo of 40 mm. Crown-Rump Length (10 Weeks).—In the 40 mm. embryo the stapes has definitely lost its simple form, and is changing from a ring-shaped to a stirrup-shaped structure (fig. 6).[7] In length it has increased to two and a quarter times that in the 22.8 mm. stage (table). The base of the stapes is irregularly triangular, the apex of the triangle pointing downward (fig. 3); its

Increase in Measurements with the Growth of the Embryo

Embryo (Crown-Rump Length, Mm.)	Measurements									
	Stapes		Base				Anterior Crus		Posterior Crus	
					Width, Mm.					
	Length, Mm.	Increase in Length*	Length, Mm.	Increase in Length*	Anterior	Posterior	Length, Mm.	Increase in Length*	Length, Mm.	Increase in Length*
22.8	0.294	....	0.248	....	0.232	0.187	0.292	....	0.284	....
29	0.408	1.39	0.408	1.64	0.24	0.20	0.369	1.26	0.348	1.22
40	0.668	2.27	0.608	2.45	0.38	0.14	0.704	2.41	0.576	2.02
135	2.32	7.89	2.48	10.0	0.904	0.816	2.208	7.54	2.032	7.15
161	2.60	8.84	3.27	13.2	1.032	0.896	2.184	7.74	2.104	7.4
183	2.84	9.65	2.60	10.5	1.176	0.856	2.536	8.68	2.384	8.39

* Ratio to 22.8 mm. embryo.

anterior (upper) part has become markedly flattened (fig. 6). The capital extremity appears as a slight prolongation. Owing to the fact that the head and base are now distinguishable, the crura appear as definite subdivisions of the stapes; set off from the original ring of cartilage by the nodular head and the flattened base, the crura, in

5. Broman, I.: (*a*) Ueber die Entwicklung der Gehörknöchelchen beim Memschen, Verhandl. d. anat. Gesellsch. **12**:230-236, 1898; (*b*) Ueber die Entwicklung der Gehörknöchelchen, Monatschr. f. Ohrenh. **25**:65, 1891.

6. Martin, J., and Anson, B. J.: Otic Capsule and Membranous Labyrinth of the 29 mm. (Crown-Rump) Human Embryo, Arch. Otolaryng. **27**:279-303 (March) 1938.

7. In form and structure the stapes of the 39.5 mm. embryo (Carnegie Collection, no. 6203) is a virtual duplication of that in the 40 mm. stage, as here illustrated in figures 3 and 6. In neither the 69 mm. nor the 85 mm. embryo in the Carnegie Collection (no. 4291 and no. 30, respectively) has bone begun to form in the stapes.

retaining their curved outline, now seem to possess the bowed form which characterizes these parts in the adult. The intercrural space is elongate, no longer circular. The capsule, as well as the stapes, is entirely cartilaginous. Although more capacious, the vestibular window still retains the roughly triangular form of the earlier stages.

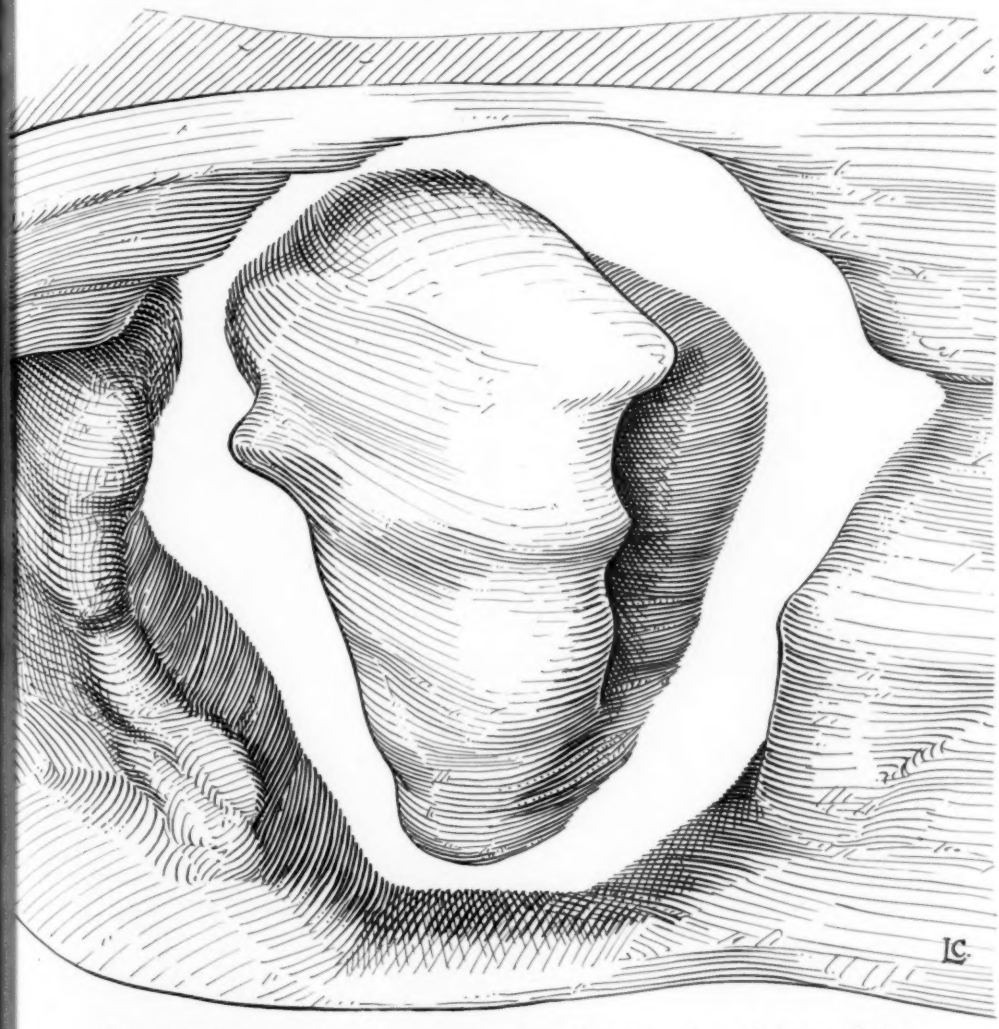
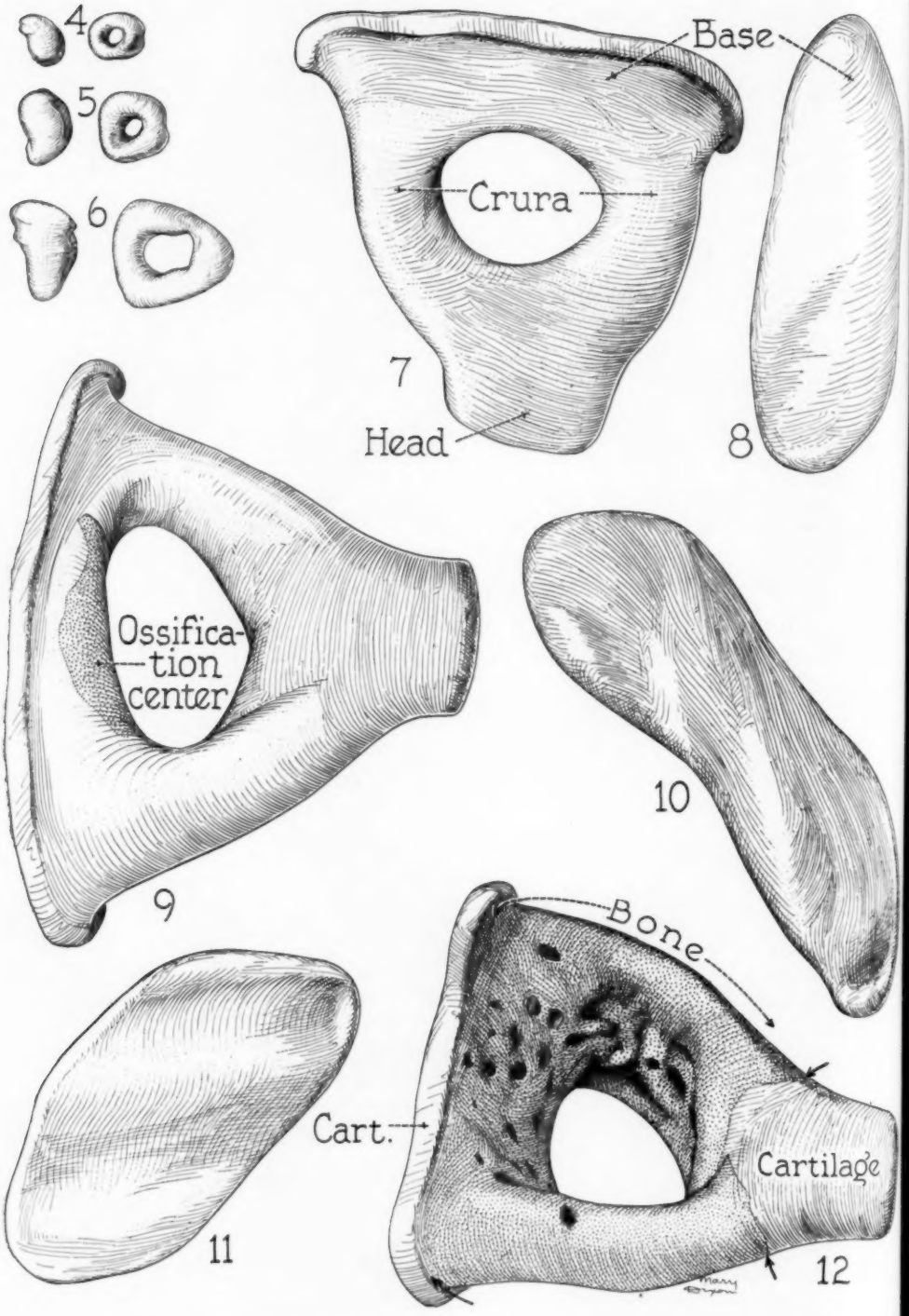


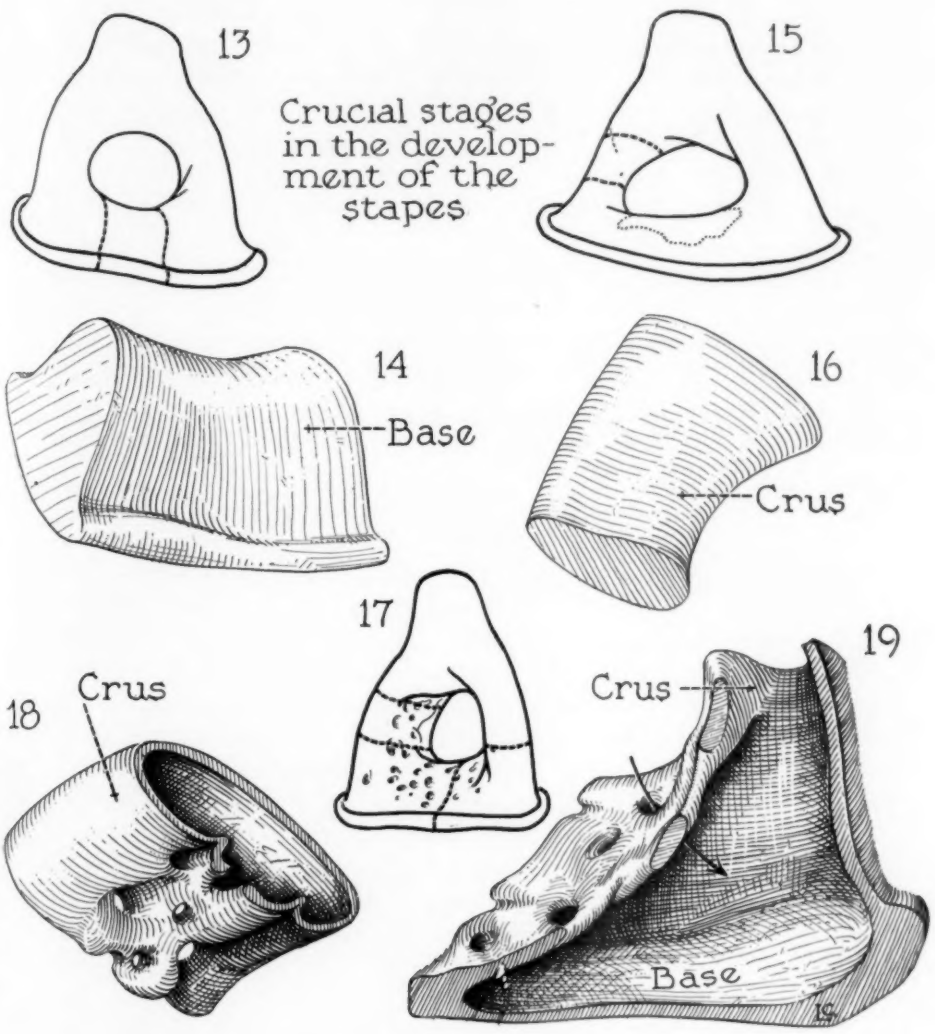
Fig. 3.—Reconstruction of the stapes and adjacent portion of the vestibular window in embryo of 40 mm.; × 214 (compare fig. 6).

Embryo of 135 mm. Crown-Rump Length (17 Weeks).—The stapes has increased considerably in size between the 22.8 mm. and the 135 mm. stage; both length and breadth are approximately eight times their initial size. The various parts of the stapes are readily identi-



Figs. 4 to 12.—Reconstructions of the stapes; vestibular and cranial views, in pairs; × 25. Figure 4, the 22.8 mm. embryo; figure 5, the 29 mm.; figure 6, the 40 mm.; figures 7 and 8, the 135 mm.; figures 9 and 10, the 161 mm., and figures 11 and 12, the 183 mm.; *Cart.* indicates cartilage.

fiable (figs. 2, 7 and 8). The base, now flattened, fits in the window closely (figs. 24 and 25) and is attached to the window through a definite stapedial ligament (figs. 26 and 27).



Figs. 13 to 19.—Figures 13, 15 and 17, reconstructions of the stapes; embryos of 135, 161 and 183 mm.; superior aspect; × 21 (compare figs. 7, 9 and 12, respectively). Figures 14, 16, 18 and 19, segments of these reconstructions taken from the areas indicated in figures 13, 15 and 17; × 42. Figure 14 represents the middle third of the base (135 mm. embryo); figure 16, the middle two fourths of the posterior crus (183 mm. embryo), and figure 19, the anterior crus and base (183 mm. embryo).

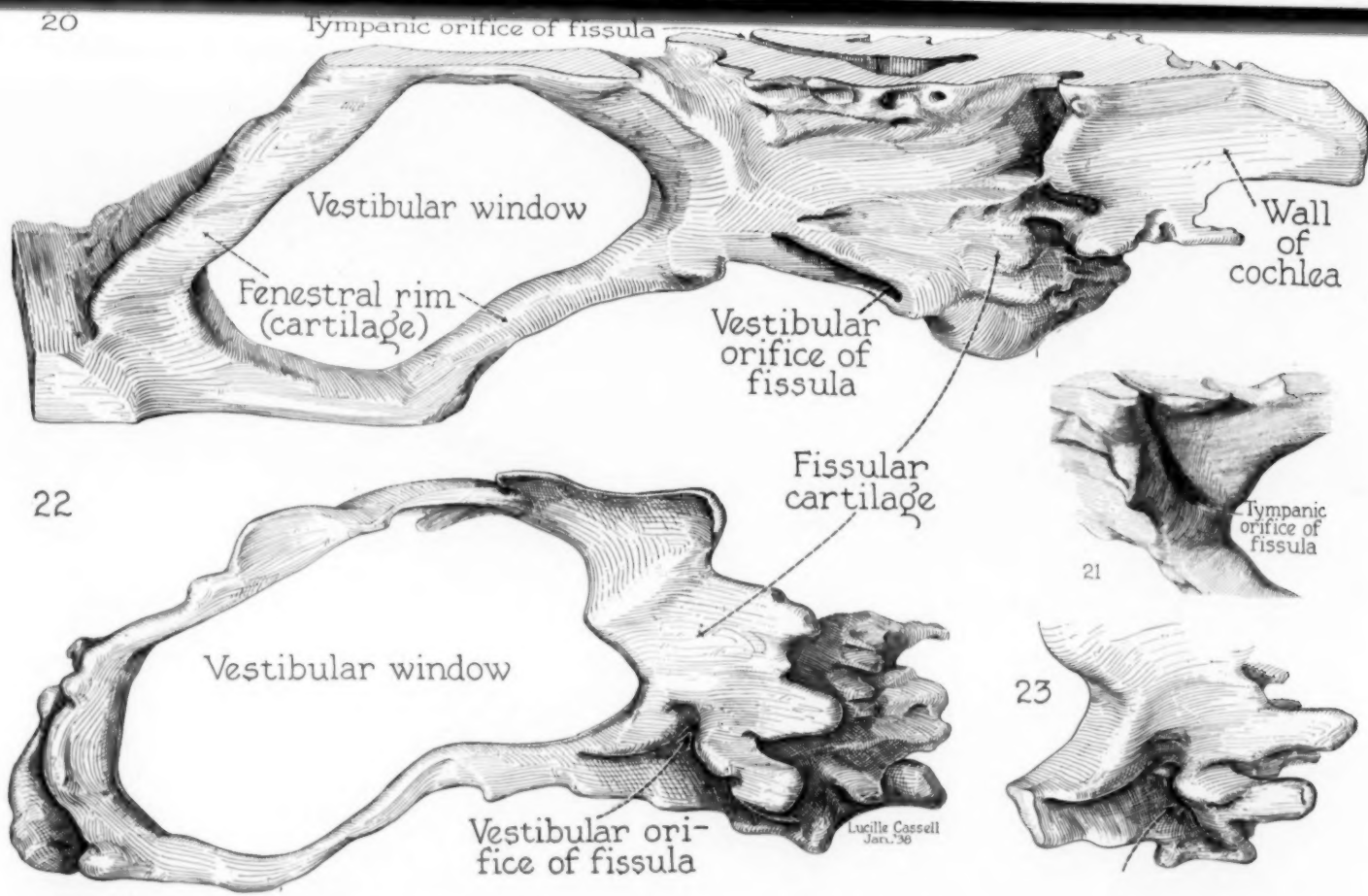
The base, like the remainder of the ossicle, is cartilaginous. The base of the stapes is flattened on its vestibular aspect and narrowed and rounded on its tympanic (figs. 13 and 14). It is lipped circumferentially (i. e., where in contact with the window), a condition which is not forecast by the conformation of the stapes in the embryo of 40 mm. The articular surface of the head is hollowed to receive the incus (fig. 25). The crura are now dissimilar, the anterior crus being the longer of the two; the crura remain solid cartilaginous bars, as does the base (fig. 14). As the crura extend laterally, they turn somewhat downward; they arise from the base nearer its inferior than its superior margin. The intercrural space is oval and its margins smooth.

The labyrinthic capsule above and below the vestibular window projects laterally; within the recess thus bounded the stapes rests. The superior ledge forms the floor of the future facial canal, in which the facial nerve follows an arching course over the vestibular window; anteriorly the same ledge will later form the semicanal for the tensor tympani muscle. The cartilage of the labyrinthic capsule is gradually being replaced by bone (Bast, 1930[2]), one center of ossification now pressing toward the vestibular window (figs. 24 and 25).

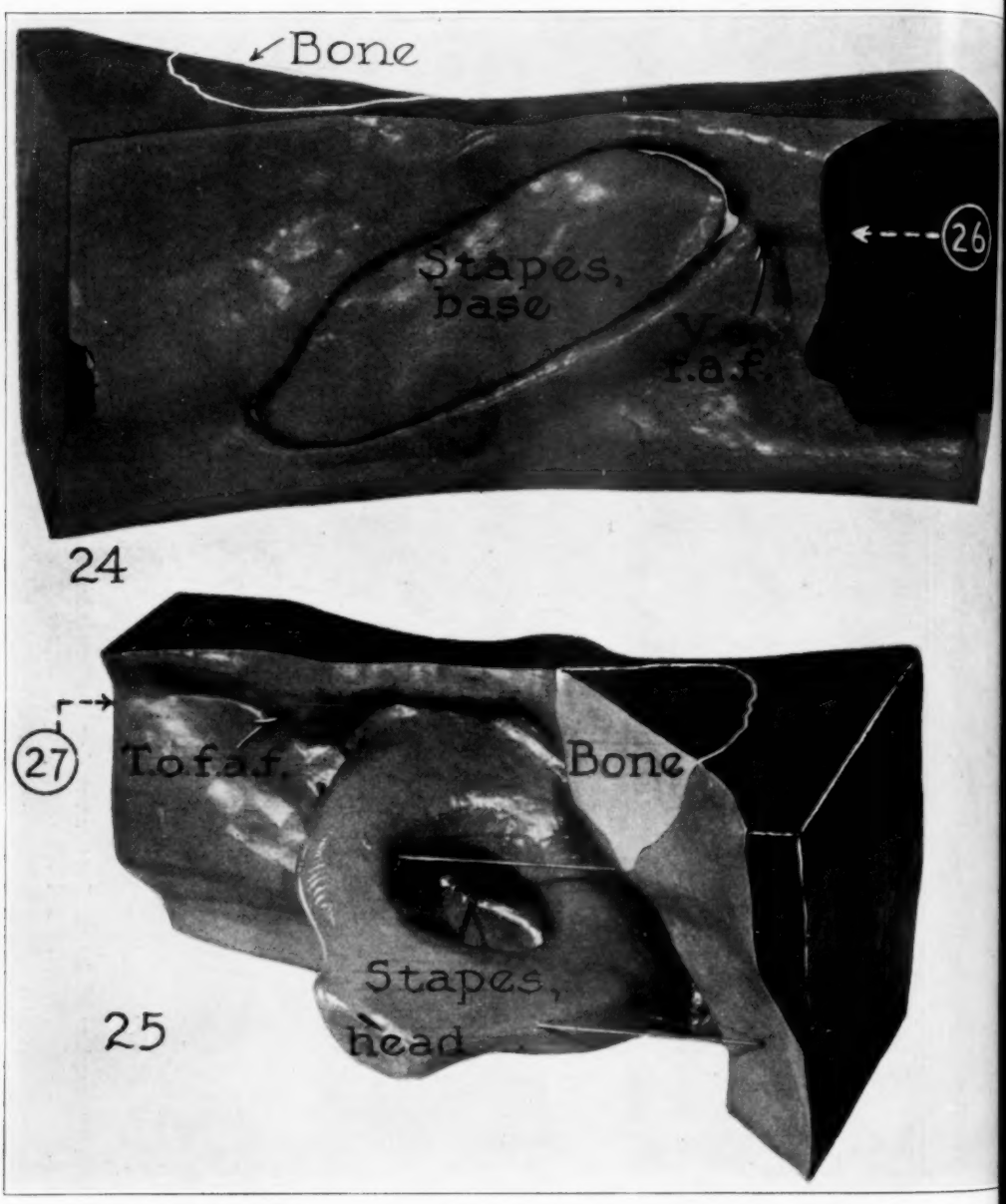
Before the capsule becomes wholly ossified, within it is formed a stripe of connective tissue reaching from the vestibular to the tympanic surface of the lateral wall of the capsule, in front of the vestibular window; this channel, the fissula ante fenestram, was first recognized as a probeable opening in the dried bone of the adult. Around the core of connective tissue the primitive cartilage remains in the form of a fenestral rim, as a remnant of the cartilaginous otic capsule. The fissula, according to Bast (1933),[8] is easily discerned in the embryo of 100 mm. (14 weeks); when the precartilaginous labyrinthine capsule changes to cartilage, the fissure remains as an area in which the precartilage undergoes a retrograde change, forming vacuolated areolar tissue and later vascular connective tissue. The vestibular orifice is regularly situated near the junction of the scala vestibuli and the vestibular cavity; the tympanic orifice is usually adjacent to the attachment of the annular ligament but occasionally may open into the semicanal for the tensor muscle. In addition to the fissula ante fenestram, a fibrous zone sometimes occurs posterior to the oval window; this is known as the fossula post fenestram. It is histologically similar to the fissula but narrower and shorter. Unlike the fissula ante fenestram, the fossula is an inconstant structure.

8. Bast, T. H.: Development of the Otic Capsule: II. The Origin, Development and Significance of the Fissula Ante Fenestram and Its Relation to Otosclerotic Foci, Arch. Otolaryng. **18**:1-20 (July) 1933.

Tympanic orifice of fissula
20

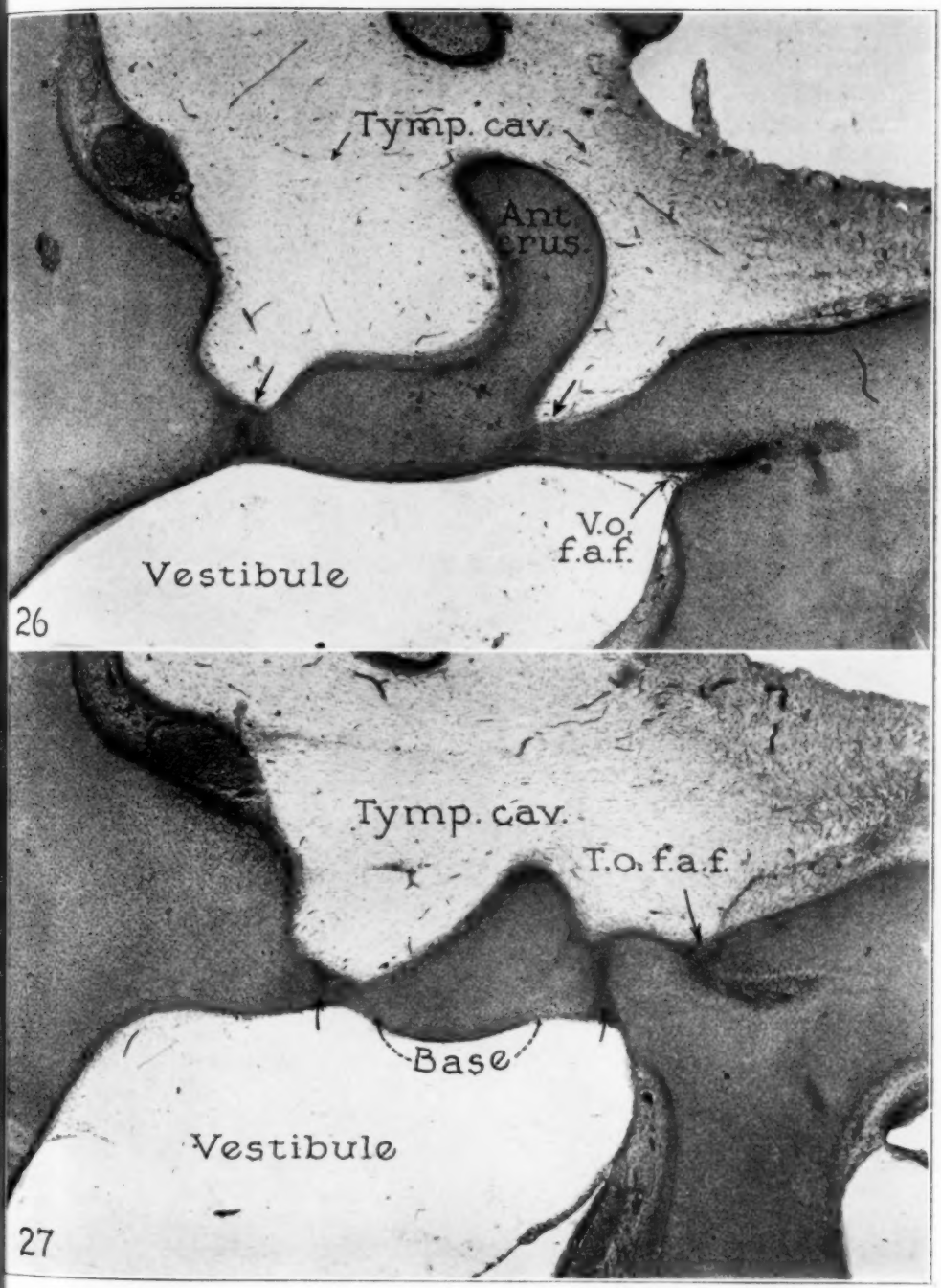


Figs. 20 to 23.—Reconstructions of the cartilage surrounding the vestibular window and the fissula ante fenestram; figures 20 and 21, embryo of 183 mm. (compare figs. 31 and 32, respectively); figures 22 and 23, person 70 years old; × 27. Figure 21 is a tympanic view; the others vestibular.



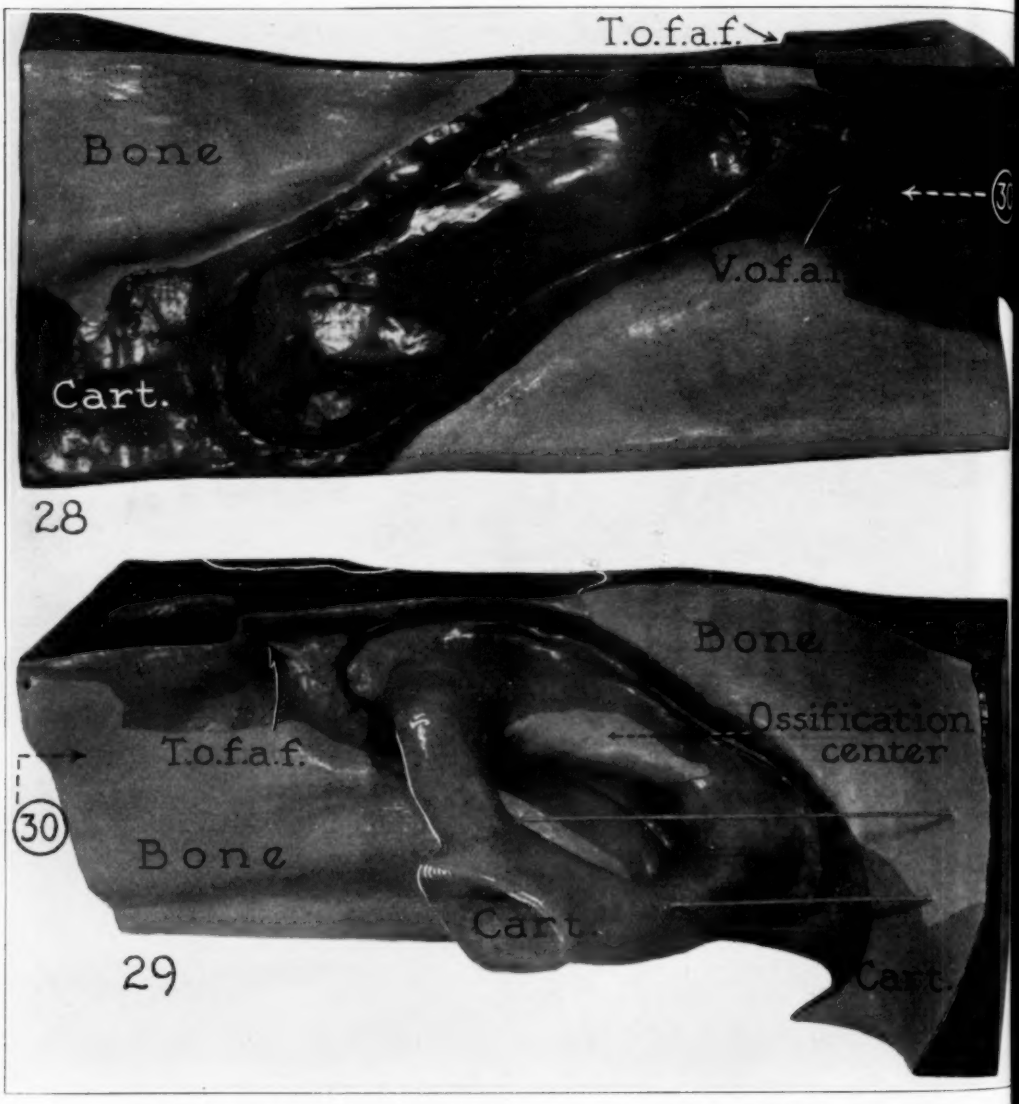
Figs. 24 and 25.—Reconstruction of the stapes and adjacent portion of the otic capsule in embryo of 135 mm.; × 28. Figure 24 is the vestibular aspect, and figure 25, the tympanic. The levels of the sections in figures 26 and 27 are indicated by lines correspondingly numbered.

In these and in the succeeding figures *Ant. crus.* indicates anterior crus; *Cart.*, cartilage; *Fen. cart.*, fenestral cartilage; *F. n.*, facial nerve; *Fiss. cart.*, fissular catilage; *Muc. memb.*, mucous membrane; *Tymp. cav.*, tympanic cavity (future); *T.o.f.a.f.*, tympanic orifice of fissula ante fenestram, and *V.o.f.a.f.*, vestibular orifice of fissula ante fenestram.



Figs. 26 and 27.—Sections through the stapes and the fissula in embryo of 135 mm.; × 31. Figure 26, vestibular orifice of the fissula; figure 27, tympanic orifice.

A prominent fissula occurs in the present specimen. Its tympanic extremity is a pronounced slit, removed by 0.25 mm. from the anterior margin of the oval window (figs. 25 and 27); the orifice is 0.2 mm.



Figs. 28 and 29.—Reconstruction of the stapes and the neighboring structures in embryo of 161 mm., showing the primary center of ossification in the stapes; × 23. Figure 28, the vestibular aspect, and figure 29, the tympanic. The level of the section in figure 30 is indicated by a correspondingly numbered line.

long and 0.07 mm. wide. Its long axis coincides with that of a sulcus in the cartilaginous capsule. The vestibular orifice is 1.6 mm. long and 0.07 mm. wide (figs. 24 and 26); only 0.12 mm. intervenes between the

orifice and the adjacent margin of the vestibular window. The opening is continuous with a sulcus which in turn spreads out on the roof of the scala vestibuli. A supernumerary orifice opens directly into the vestibular window; it is 0.1 mm. long and 0.05 mm. wide.

Embryo of 161 mm. Crown-Rump Length (19½ Weeks).—The length of the stapes is now eight and one-half to nine times as great as it was in the 22.8 mm. embryo (figs. 9 and 10; compare fig. 4). The outline of the base is somewhat reniform; the edges are smooth. The entire vestibular surface of the base is cartilaginous, but on the tympanic aspect a center of ossification is present (figs. 9, 29 and 30). Broman (1891)[5] expressed the belief that ossification began at a later stage (210 mm.). The long axis of the center corresponds to that of the head of the stapes. The base, at its fenestral margin, is cupped backward toward the vestibule, forming a prominent circumferential lip (fig. 9). It fits the vestibular window snugly (fig. 24).

The crura have not undergone striking change in shape. They remain solid cartilaginous masses (figs. 15 and 16). The head is acquiring the familiar shape of the adult ossicle, and a definite neck is distinguishable. The articular surface of the head is concave and points slightly downward. Both head and neck are entirely cartilaginous. The intercrural space is not yet triangular in outline. Urbantschitsch (1876)[9] expressed the belief that the ossicles do not attain their definitive size until the time of birth; actually, adult lengths are attained at this stage (161 mm.), in midfetal life.

The fissula ante fenestram is now a prominent channel through the cartilaginous otic capsule. The tympanic orifice is situated on the floor of an oblique sulcus (fig. 29), deeper than that seen in the preceding stage. The orifice is circular and small, measuring 0.1 mm. in diameter; it is removed by 0.6 mm. from the anterior margin of the vestibular window. Midway in its course the fissure abruptly expands; after having extended for 1.2 mm. beyond the fenestral margin, it turns backward and downward to end at a vestibular orifice (figs. 28 and 30) placed 0.4 mm. anterior to the window. This also is small, measuring 0.3 mm. in length and 0.2 mm. in width; it opens on the roof of the scala vestibuli.

On the medial tympanic (fig. 29) and the lateral vestibular wall (fig. 28), bone has spread toward the vestibular window from above and below, so that only the fenestral area of the capsule in this region remains cartilaginous. On the tympanic wall the bone comes within 0.5 mm. of the fenestral opening; on the vestibular wall, within 1.8 mm.

9. Urbantschitsch, V.: Zur Anatomie der Gehörknöchelchen der Menschen, Arch. f. Ohrenh. **2**:1-10, 1876.

So restricted, in fact, has the cartilage become that it begins to assume the form of a shell lining the vestibular window—a shell with two extensions, one directed posteriorly and the other anteriorly. The fissula is lodged in the anterior part, entirely embedded in cartilaginous tissue.

Fetus of 183 mm. Crown-Rump Length (21 Weeks).—Developmental changes taking place between the preceding (161 mm.) and the present (183 mm.) stage are of a crucial nature; they affect both form and histologic structure of the stapes.

Surprisingly, the stapes is somewhat smaller than the ossicle in the 161 mm. embryo; the base is shorter and wider (fig. 11; compare fig. 10). This difference is apparent also in the earlier reconstructions by Bast (1930,[2] figs. 34 and 35); as we have recently observed, how-

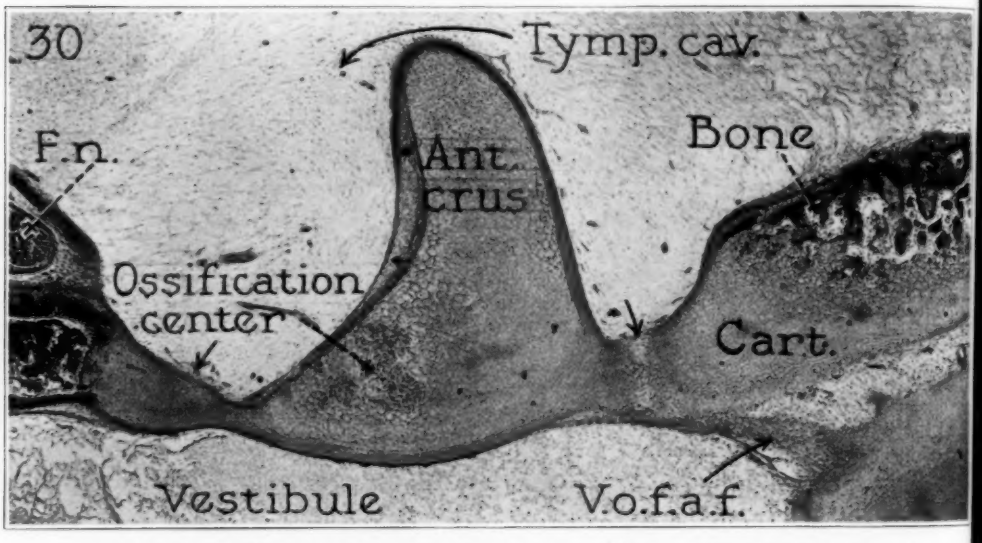


Fig. 30.—Section through the stapes and the vestibular extremity of the fissula in embryo of 183 mm.; × 31.

ever, the adult stapes varies considerably in size, in some cases being smaller than it is in the 19 week embryo.

In form also the stapes of the 183 mm. embryo evidences striking changes. The base, at its periphery, is elevated into an even more prominent flangelike projection (fig. 12). The crura are not circular in cross section but of flattened oval form, the greater dimension being the vertical one (figs. 17 and 18). The compressed surface is that which faces the intercrural space. The head and neck of the stapes are longer, an alteration which renders the configuration distinctly stapedial. The intercrural space is not yet exactly triangular, owing to the manner in which the crura expand gradually at their capital extremities to meet the base.

Although the vestibular portion of the base, its articular rim and the head and neck of the stapes remain cartilaginous (figs. 11 and 12), all of the tympanic surface of the base and the two crura have changed to bone (figs. 18 and 19). The crura and the base of the stapes, now markedly thinned, are on their internal surface extensively perforate (figs. 12, 18 and 19); through these fenestrations pass vessels from the surrounding vascular mesenchyma to the cavity within the stapes (figs. 34 and 35). This mechanism of replacement of cartilage brings the stapes into the category of long bones generally, the ossicle being essentially a bone of minute size, in which the original solid cartilaginous bar has been replaced by an osseous shell which encloses a space. The space contains primitive marrow, which is supplied by a large number of vessels.[10]

As in the preceding stage, the base almost fills the vestibular window and conforms to it closely in outline (figs. 31 to 33). The tissue bounding the window is cartilage, a ring of that tissue being visible on the tympanic (figs. 32 and 33) and the vestibular (fig. 31) surface of the fenestral portion of the capsule. As in the 161 mm. embryo, this fenestral ring is continuous with a seam of cartilage which extends anterosuperiorly and posteroinferiorly from the vestibular window; within the former lies the fissula ante fenestram (figs. 20 and 21).

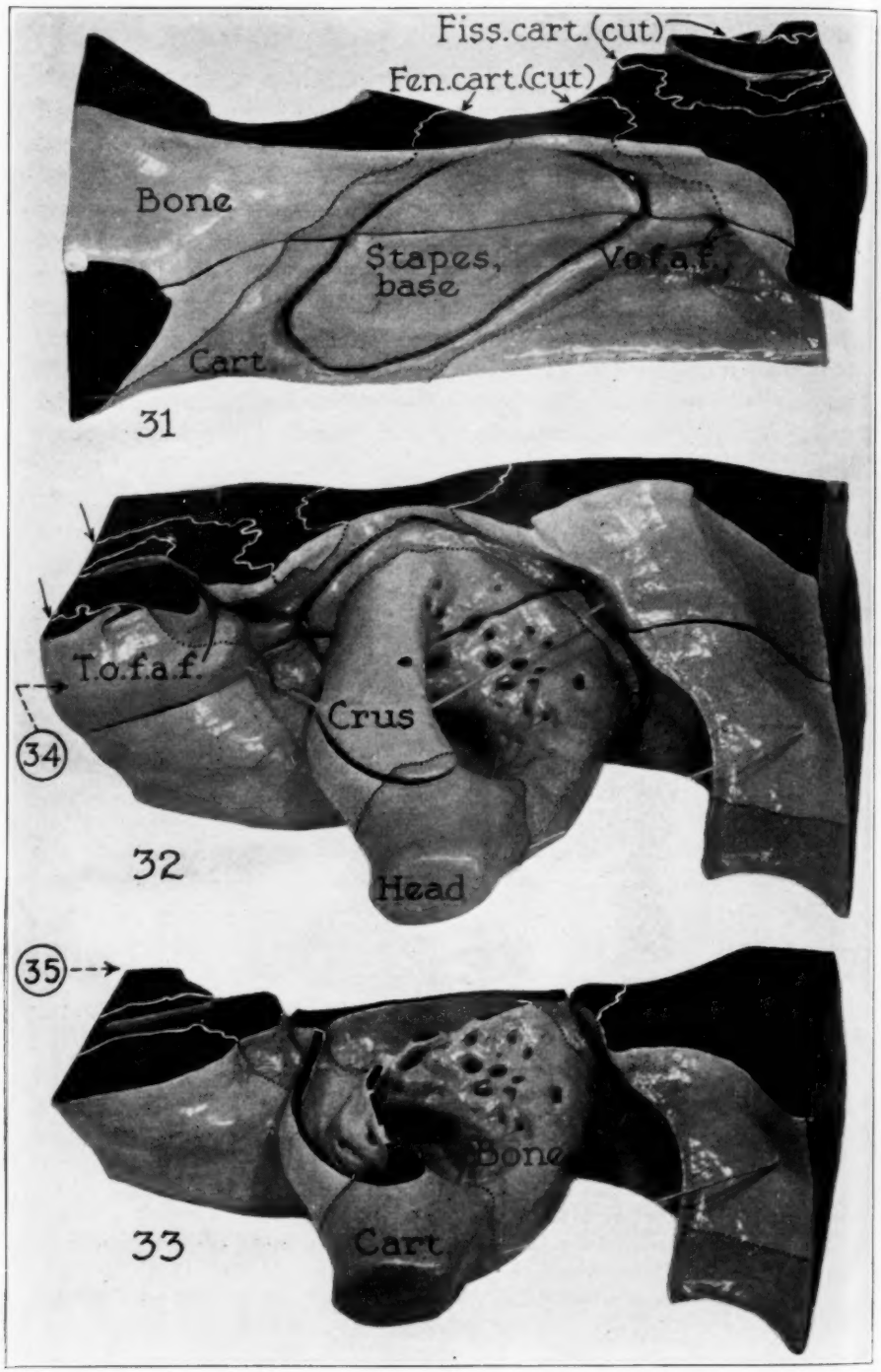
The orifices of the fissula have increased considerably in size. But the growth of the fissula as a whole has not kept pace with that of the otic capsule in which it is lodged, being at this stage only one sixth again as long as it is in the embryo of 161 mm.; such differences are doubtless attributable to individual variation (Anson and Martin, 1935;[11] Wilson, 1935[12] Bast, 1936[13]). The tympanic opening, although incompletely reconstructed, is 0.27 mm. long (in the obliquely vertical direction) and 0.01 mm. wide; the sulcus from the floor of which the fissure extends into the capsule is more prominent than in the earlier stages (figs. 21 and 32). Owing to its oblique course, the posteroinferior limit of the orifice is 0.5 mm. removed from the anterior margin of the vestibular window and the anterosuperior limit 0.9 mm. therefrom. Within the capsule the fissular space widens somewhat as

10. As will be described fully in a later publication, the internal wall of the crus and of the base is ultimately resorbed, each part then resembling a long bone of diminutive size one side of which has been destroyed and its marrow tissue replaced by periosteum.

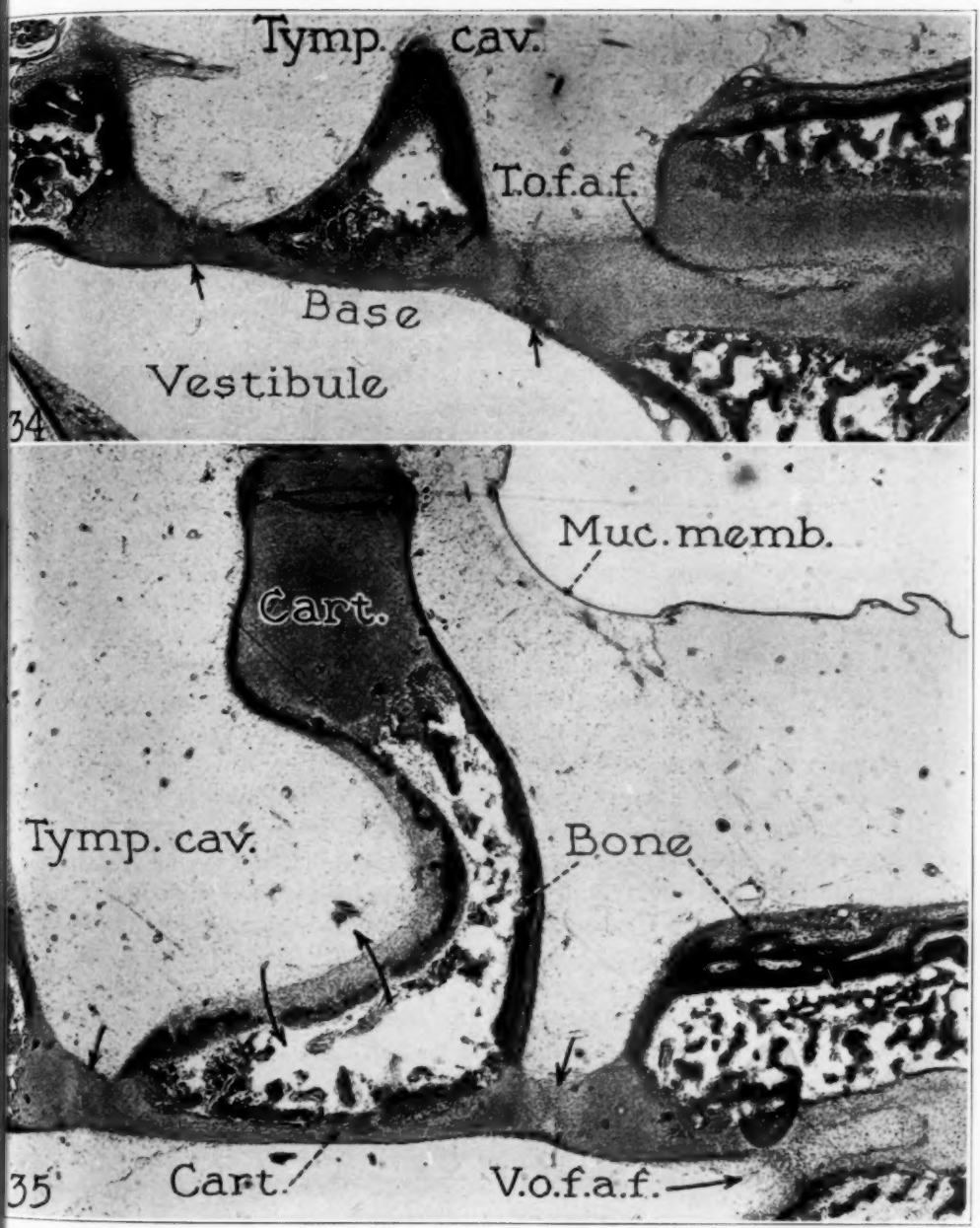
11. Anson, B. J., and Martin, J., Jr.: Fissula Ante Fenestram: Its Form and Contents in Early Life, Arch. Otolaryng. **21**:303-323 (March) 1935.

12. Wilson, J. G.: Fissula Ante Fenestram and the Adjacent Tissue in the Human Otic Capsule, Acta oto-laryng. **22**:382-389, 1935.

13. Bast, T. H.: Development of the Otic Capsule: III. Fetal and Infantile Changes in the Fissular Region and Their Probable Relationship to the Formation of Otosclerotic Foci, Arch. Otolaryng. **23**:509-525 (May) 1936.



Figs. 31 to 33.—Reconstruction of the stapes and neighboring area in embryo of 183 mm.; × 20. Figure 31, the vestibular aspect, and figures 32 and 33, the tympanic. Figure 33 shows the upper section of the reconstruction removed to reveal the cavity within the crura and the base of the stapes. The levels of the sections in figures 34 and 35 are indicated by lines correspondingly numbered.



Figs. 34 and 35.—Sections through the stapes and the fissula in embryo of 183 mm.; × 31. Figure 34, the tympanic orifice of the fissula, and figure 35, the vestibular orifice. Curved arrows pass through the fenestrations (compare figs. 12, 19, 32 and 33).

it extends to a depth of 1.4 mm. (fig. 33); then, turning backward and downward, it terminates in a vestibular orifice (figs. 20 and 31), which, like the corresponding orifice in the preceding specimen, is situated at the junction of the vestibule and the scala vestibuli; it is removed 0.3 mm. from the window. The vestibular orifice is elongate, being 0.7 mm. long and 0.1 mm. wide (fig. 20). Throughout its course, from tympanic to vestibular orifice, the connective tissue lies within cartilage (figs. 34 and 35; compare fig. 20).

A fossula post fenestram is present.

In this specimen bone has replaced cartilage to such an extent that the latter tissue remains only in the general region of the vestibular window. Anteriorly, the cartilage reaches the cochlea, part of whose wall it forms (fig. 20).

This elongate seam of cartilage, which now constitutes a relatively small part of the lateral wall of the otic capsule, represents in reduced form that larger mass which, at the 135 mm. stage, makes up a considerable part of the fenestral area (figs. 24 and 25; compare Bast, 1930[2]). Encroached on by bone from above and below, the mass persists as a rim surrounding the vestibular window; it extends anterosuperiorly to enclose the fissula (figs. 20 and 21) and posteroinferiorly to include the fossula; it assumes the form of an oval shell with two bulbous enlargements, a larger fissular and a smaller fossular part. Viewed as a whole, then, it may be said to be the cartilaginous remnant which encloses the three orifices in the lateral capsular wall—one, an oval window in which rests the stapes and the other two, small fissure-like communications, each filled with vascular connective tissue. The entire mass lies in an oblique plane which coincides with the long axis of the stapes itself. Further encroached on by bone as embryonic development and adult alteration progress, it retains more than a semblance of its original form even in persons of advanced age (figs. 22 and 23).

As will be shown in a later publication, the cartilage is soon replaced by bone at the cochlear extremity, the anterior part of the mass then persisting as a shell for the fissula, not as a mass between fenestral area and cochlea. Gradually reduced in amount, that part which surrounds the tympanic end of the fissula may be totally obliterated in the adult, no trace of it remaining within the bone of the tympanic wall, while that which encloses the vestibular end regularly persists (figs. 22 and 23); whether slight or massive, histologically it remains a typical hyaline cartilage. One might therefore describe the fissular area as one in which histogenetic changes occur slowly; the primitive cartilaginous tissue retains potentialities for growth, the newly formed tissue derived from the original cartilage sometimes replacing the connective tissue of

the fissula and even protruding from the normal orifices of the fissula (Anson and Martin, 1935,[11] figs. 67 to 69; Bast, 1936,[13] figs. 47 to 50).

In the infant, the child and the adult either orifice of the fissula may open into a sulcus in the bone (Anson and Martin, 1935,[11] fig. 1); the tympanic sulcus is frequently rather elongate, curving downward and backward toward the anterior margin of the vestibular window. The presence of such a sulcus is foreshadowed in the present stage (fig. 32) as it is also in the preceding one (161 mm., fig. 29). A less pronounced sulcus is present at the vestibular extremity (figs. 31 and 28). In the adult and even in the infant and child, the vestibular orifice is regularly longer than the tympanic (Anson and Martin, 1935,[11] figs. 2, 6, 10, 15, 18, 22 and 28); this condition is not forecast in the embryonic stages (135, 161 and 183 mm.), in which the cleft is still totally surrounded by cartilage; it is probably established when bone encroaches on the fissular cartilage.

CONCLUSIONS

The stapedial cartilage is clearly defined in the embryo of 22.8 mm.; at this stage it possesses the form of a ring, not that of a stirrup. At the 40 mm. stage its constituent parts are distinguishable, the somewhat flattened base being set off from the bowed crura; no true neck and head are present. Between the 40 and the 135 mm. stage pronounced changes have occurred, which convert the simple structure into one definitely stirrup-like. In the 135 mm. embryo the stapes is still cartilaginous, but at the 161 mm. stage a center of ossification has formed, situated in the basal portion. Remarkably enough, while still almost entirely chondral, the stapes comes close to attaining adult size. The stapes is a far more bulky structure at this stage than it is in the adult. Irregular in outline in earlier stages, the margin of the base is smooth in the embryo of 135 mm.

The base of the stapes has attained adult size and shape in the embryo of 161 mm., but it is destined to undergo series of structural changes throughout life. In the 22.8, the 29 and the 40 mm. stage the base is cartilaginous. At the 161 mm. stage the first center of ossification has appeared on the tympanic surface of the base; thereafter changes in structure occur rapidly. The bulky base becomes hollowed and acquires a marrow cavity and a fenestrated internal surface; the vestibular layer remains cartilaginous. In later stages the fenestrated internal wall disappears, and the base is reduced to a relatively flat plate, cartilaginous on the vestibular and osseous on the tympanic surface.

The crura also reach their definitive size in the 161 mm. embryo. Their development may be likened to that of any long bone. They are at first solid cartilaginous structures; cartilage is then invaded by

vascular osteogenic buds, which gradually resorb the embryonic cartilage, beginning at the base and spreading toward the head. This resorption progresses so rapidly that in the 183 mm. embryo the crura are hollow bony cylinders, perforated by vessels along their concave (internal) surface. The crura contain a marrow cavity continuous with that of the base.

The head and neck are ossified later than the crura; they are still cartilaginous in the 183 mm. embryo. The osseous tissue develops from a single center, situated on the tympanic aspect of the base in the 161 mm. embryo, and spreads therefrom along the base and the crura until cartilage finally remains only on the vestibular aspect of the base and the head and neck of the ossicle; concurrently the osseous portions are hollowed, and there is a continuous cavity filled with marrow-like tissue; the appearance is that of a long bone, diminutive in size, with a cartilaginous articular extremity. On the internal surface of the base, the bone, like that of the corresponding aspect of each crus, is riddled by vascular hiatuses, the openings suggesting multiple nutrient foramens; the external surface of the crus is smooth bone, while that of the vestibular surface of the base is unaltered cartilage. Intrinsic spaces within the base and the crura—haversian spaces—are not yet present; in older specimens these traverse the bone and communicate with vessels in the subepithelial tissue.

The vestibular window reaches its definitive shape and size in the embryo of 161 mm., at that stage conforming to the shape of the base of the stapes. The shape of the window in the earlier stages is irregularly triangular, the base of the stapes being relatively much smaller than the fenestral space. As early as the 183 mm. stage, changes toward the adult form occur; the posterior half of the vestibular window remains flattened and in close proximity to the posterior surface of the base, while the anterior half becomes sharp and tapered, thereby causing an overriding of the base on the tympanic surface of the labyrinthine capsule. The vestibular window is lined by a rim of cartilage throughout life; this fenestral cartilage decreases as age advances, the cartilaginous rim in the 70 year old person being approximately one half as thick as that in the 183 mm. embryo; yet the cartilage of this articular surface is never wholly replaced by bone.

The fissula ante fenestram and the fossula post fenestram (when present) are surrounded by cartilage which is directly continuous with the vestibular cartilaginous rim. The entire mass thus formed is larger at the anterior than at the posterior extremity, since the fissular investment of cartilage is thick in fetal stages. The fissula has not appeared in the 40 mm. embryo but is present in the one of 135 mm. In all cases the tympanic extremity of the fissula ante fenestram is placed

more superiorly than is the vestibular; the latter is usually the larger of the two and the closer to the vestibular window; there may be a third extremity opening directly into the vestibular window. The embryonic cartilaginous shell of the fissula persists, in part at least, throughout life.

The fossula post fenestram, an inconstant channel situated posterior to the vestibular window, occurred in but 1 of the 3 older specimens studied; here it lay within a posterior projection of the fenestral shell of cartilage, which was considerably smaller than the chondral covering for the fissula in the same specimen.[14]

14. Since the present paper left the author's hands, an excellent account of the fossula post fenestram, by Professor T. H. Bast, has appeared in the April 1938 issue of the ARCHIVES. pages 402 to 412. In development and in structure the fossula was discovered to be generally similar to the fissula ante fenestram, being an evagination of vestibular tissue into the bony capsule. But, less frequent in occurrence than the fissula, the fossula was present in 67 per cent of the ears studied; in 25 per cent of the ears possessing a fossula, the channel was complete, that is, extended from the vestibule to the tympanic cavity; in 1.67 per cent, it opened on the tympanic cavity only; in the remaining 73.3 per cent, the opposite, or vestibular, orifice alone was found.

USE OF SULFANILAMIDE IN OTOLARYNGOLOGY

A REVIEW OF THE LITERATURE

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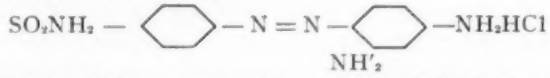
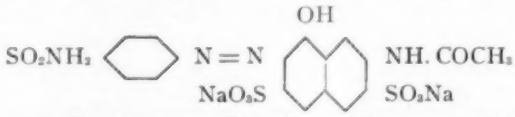
DEFINITION OF TERMS

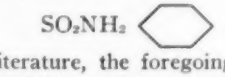
The original prontosil, the hydrochloride or 4-sulfamido-2′, 4′-diaminazobenzene, is an azo dye. This red crystalline powder has a melting point of 247 to 251 C. and is soluble in water up to about 0.25 per cent.



Prontosil soluble [1] is a 2.5 per cent watery solution of disodium-4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate, which is a reddish crystalline material and soluble up to about 4 per cent in water.



Sulfanilamide was selected by the Council on Pharmacy and Chemistry of the American Medical Association as the name for paraaminobenzenesulfonamide. This white crystalline powder has a melting point of 165 C. and is soluble in water up to about 1 per cent.



In citations of the literature, the foregoing terminology has been adhered to wherever it has been possible to determine which preparation was used. When the term "prontosil" was used in a report and no information permitting identification of the particular preparation was given, a parenthetic statement has been inserted to that effect.

INTRODUCTION

Although considerable confusion still exists concerning the therapeutic usefulness of sulfanilamide and its related compounds, a wealth of experimental and clinical data has accumulated. The following review of the literature deals only with those problems which are of interest to the otolaryngologist but necessarily includes experience gained in the laboratory and in other fields of medicine.

HISTORICAL SURVEY

In 1908 Gelmo,[1a] while working on the chemistry of azo dyes, as stated by Schulte,[2] first mentioned paraaminobenzenesulfonamide. The

1. Recently the manufacturer has adapted the name neoprontosil for this substance, and the Council on Pharmacy and Chemistry of the American Medical Association has concurred.

(Footnotes continued on next page)

sulfonamide grouping was first incorporated in azo dyes by Hoerlein, Dressel and Kothe,[3] who also substituted sulfonamido groups; it was noted at that time that the ability of these dyes to enter into intimate combination with wool proteins is greater than that of similar dyes free from sulfonamide.[4] In 1911, Sisley and Porcher[5] demonstrated that bacterial action in the intestine breaks down chrysoidine (diaminoazobenzene hydrochloride), which splits at the double bond. As early as 1913, Eisenberg[6] observed the bactericidal power of certain azo dyes in vitro and considered the possibility of employing chrysoidine in therapeutics.

In 1914, chrysoidine being used as a basis for the work,[2] pyridium (benzeneazo-α-α-diaminopyridine hydrochloride) was synthesized.[7] The synthesis of toluylazotoluylazo-β-naphthol and diacetylaminoazotoluene followed.[8] Accomplishing the synthesis of metaaminobenzenesulfonamide, metaacetylaminobenzenesulfonamide and parachloroacetylaminobenzenesulfonamide in 1917, Jacobs and Heidelberger[9] turned their attention to azo dyes derived from hydrocupreine and hydrocupreidine[10] and demonstrated that hydrocupreine and hydrocupreidine yield well defined azo dyes with diazotized aromatic amines. They subsequently synthesized paraaminobenzenesulfonamideazohydrocupreine, metaaminobenzenesulfonamideazohydrocupreine and parabenzenesulfanilicazohydrocupreine and noted that many of these substances were bactericidal in vitro.

1a. Gelmo, P.: Ueber Sulfamide der p-Amidobenzolsulfonsäure, J. f. prakt. Chem. **77**:369 (April 3) 1908.

2. Schulte, T. L.: History of the Development of Sulfanilamide, Proc. Staff Meet., Mayo Clin. **13**:53 (Jan. 26) 1938.

3. Cited by Hoerlein, H.: New Class of Chemotherapeutic Agents Against Streptococci, with Special Reference to Prontosil and Prontylin, M. Rec. **146**: 11 (July 7) 1937.

4. Welch, A. DeM.: The Pharmacologic Basis for Sulfanilamide Therapy, J. Pediat. **11**:159 (Aug.) 1937.

5. Sisley, P., and Porcher, C.: Du sort des matières colorantes dans l'organisme animal, Compt. rend. Acad. d. sc. **152**:1062, 1911.

6. Eisenberg, P.: Untersuchungen über halbspezifische Desinfektionsvorgänge, Centralbl. f. Bakt. (Abt. 1) **71**:420, 1914.

7. Tchichibabin, A. E., and Zeide, O. A.: Zhur. russk. fiz.-khim. Obsh. **46**: 1216, 1914.

8. Collins, G. W.: Chemical Examination of "Pyridum" and "Mallophene," J. Am. Pharm. A. **20**:455 (May) 1931.

9. Jacobs, W. A., and Heidelberger, M.: Amides, Uramino Compounds and Ureides Containing an Aromatic Nucleus, J. Am. Chem. Soc. **39**:2418 (Nov.) 1917.

10. Heidelberger, M., and Jacobs, W. A.: Syntheses in the Cinchona Series: III. Azo Dyes Derived from Hydrocupreine and Hydrocupreidine, J. Am. Chem. Soc. **41**:2131 (Dec.) 1919.

An azo dye synthesized for the dye industry in 1932 by Mietzsch and Klarer [3] was used experimentally in the same year in the treatment of streptococcic infections in mice by Domagk.[11] This drug (the hydrochloride of 4-sulfamido-2′, 4′-diaminoazobenzene) was the original preparation called prontosil. The observations of Domagk in 1935 indicated the therapeutic possibilities of azo compounds containing the sulfonamide radical in the para position, and his work in animals was partially or completely confirmed by subsequent investigators.[12]

The first report of the clinical use of these products was that of Foerster [13] in 1933. He reported the survival and cure of an infant with perifolliculitis and staphylococcic septicemia when prontosil soluble (streptozon) was administered. In 1934, Grütz [14] reported the cure of exudative erythema multiforme by the use of the original prontosil (D 5214) and described the effectiveness of the original prontosil administered by mouth and of prontosil soluble administered by the intravenous route in certain cases of toxic and septic erythema.[15]

Up to 1935 no experimental data concerning the prontosils had been reported,[16] but with Domagk's [11] report on the use of the original prontosil in the treatment of experimental streptococcic infections of mice clinical papers dealing with the use of the dyes in various types of infectious processes appeared. In general, good therapeutic results were obtained with the use of the original prontosil in tablets and in

11. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsche med. Wchnschr. **61**:250 (Feb. 15) 1935.

12. (*a*) Tréfouël, J.; Tréfouël, J. (Mme.); Nitti, F., and Bovet, D.: Activité du p-amino-phénylsulfamide sur les infections streptococciques expérimentales de la souris et du lapin, Compt. rend. Soc. de biol. **120**:756 (Nov.) 1935. (*b*) Levaditi, C., and Vaisman, A.: Action curative du chlorhydrate de 4-sulfamido-2, 4-diaminoazobenzene et de quelques dérivés similares, dans la streptococcie expérimentale, ibid. **119**:946, 1935. (*c*) Nitti, F., and Bovet, D.: Action du 4-sulfonamide-2-4 diaminobenzol (prontosil) sur des infections streptococciques de la souris provoquées par des streptocoques d'origine humaine, ibid. **119**:1277, 1935. (*d*) Hoerlein, H.: Mangelhafter Schutz deutschen geistigen Eigentums auf therapeutischem Gebiet, Deutsche med. Wchnschr. **61**:1090 (July 5) 1935. (*e*) Colebrook, L., and Kenny, M.: Treatment of Human Puerperal Infections, and of Experimental Infections in Mice, with Prontosil, Lancet **1**:1279 (June 6) 1936. (*f*) Long, P. H., and Bliss, E. A.: Para-Aminobenzenesulfonamide and Its Derivatives: Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcic Infection; Preliminary Report, J. A. M. A. **108**:32 (Jan. 2) 1937.

13. Foerster, L.: Sepsis in Anschluss an ausgedehnte Periporitis Heilung durch Streptozon, Zentralbl. f. Haut- u. Geschlechtskr. **45**:549, 1933.

14. Grütz, O.: Beitrag zur Kenntnis der infektiös-toxischen, Erythema-exsudativum-multiforme- ähnlichen Exantheme, Med. Klin. **30**:52 (Jan. 12) 1934.

15. Grütz, O.: Erythema exsudativum bullosum faciei, colli et extremitatum, Zentralbl. f. Haut- u. Geschlechtskr. **49**:300, 1934.

16. Long, P. H., and Bliss, E. A.: The Clinical Use of Sulfanilamide and Its Derivatives in the Treatment of Infectious Diseases, Ann. Int. Med. **11**:575 (Oct.) 1937.

solution in the treatment of streptococcic thrombophlebitis, adenitis, otitis media, erysipelas, puerperal sepsis and infectious arthritis.[17] Numerous communications followed in the German literature; the use of the original prontosil in tablets and in solution appeared to produce good results in the treatment of infections with Escherichia coli,[18] in pneumococcic and staphylococcic infections,[19] in Hodgkin's disease,[20] in sepsis [21] and especially in all cases of pure streptococcic and puerperal sepsis.[22] Schreus [17b] and Fuge [22] expressed the opinion that staphylococcic infections were not benefited. Roth [23] recognized the value of the new drugs in dealing with hemolytic streptococcic infections, and Schranz [24] reported on a series of 60 patients with sepsis, of whom 57 recovered under treatment with the original prontosil. Three of 9 patients with purulent meningitis recovered when treated with prontosil (preparation not stated) by Riecke.[25] Good results from the use of the original prontosil and of prontosil soluble in 23 cases of erysipelas were reported by Kramer,[26] and Scherber [27] used the original prontosil in the treatment of pemphigus vulgaris.

The first clinical report in France appeared in 1935. In that year, Girard [28] synthesized a compound (sulfonamidochrysoidine, also called rubiazol or French prontosil), which was apparently identical with the

17. (*a*) Klee, P., and Römer, H.: Prontosil bei Streptokokkenerkrankungen, Deutsche med. Wchnschr. **61**:253 (Feb. 15) 1935. (*b*) Schreus, H. T.: Chemotherapie des Erysipels und anderer Infektionen mit Prontosil, ibid. **61**:255 (Feb. 15) 1935. (*c*) Anselm, E.: Unsere Erfahrungen mit Prontosil bei Puerperalfieber, ibid. **61**:264 (Feb. 15) 1935. (*d*) Gantenberg, R., abstracted, ibid. **61**: 284 (Feb. 15) 1935.

18. Imhauser, K.: Ueber die Behandlung septischer Erkrankungen mit Prontosil, Med. Klin. **31**:282 (March 1) 1935.

19. Recknagel, K.: Erfahrungen mit Prontosil, München. med. Wchnschr. **82**:704 (May 2) 1935.

20. Bingold, K.: Erfolgreiche Behandlung von Hodgkin-Wechsel-Fieber mit Prontosil, München. med. Wchnschr. **82**:871 (May 30) 1935.

21. Einhauser, K.: Sepsisbehandlung mit Prontosil, München. med. Wchnschr. **82**:1263 (Aug. 2) 1935; Deutsche med. Wchnschr. **61**:1463 (Sept. 6) 1935.

22. Fuge, K.: Die Behandlung der Puerperalsepsis mit Prontosil, Deutsche med. Wchnschr. **61**:1672 (Oct. 18) 1935.

23. Roth, A.: Heilung eines Falles von Streptokokkensepsis unter Prontosilbehandlung, Deutsche med. Wchnschr. **61**:1734 (Oct. 25) 1935.

24. Schranz, H.: Zur Sepsisbehandlung mit Prontosil, München. med. Wchnschr. **82**:419 (March 14) 1935.

25. Riecke, H.: Zur Therapie der Meningitis, Ztschr. f. Hals-, Nasen- u. Ohrenh. **38**:175, 1935.

26. Kramer, W.: Ueber Erfahrungen bei der Erysipelbehandlung mit Prontosil, München. med. Wchnschr. **83**:608 (April 10) 1936.

27. Scherber, G.: Die Behandlung des Rotlauf mit interner Prontosiltherapie kombiniert mit intravenösen Omnadininjektionen, Wien. med. Wchnschr. **85**:783 (July 6) 1935; Zur Behandlung der verschiedenen Formen des Pemphigus chronicus mit Antileprol und Prontosil, ibid. **86**:22 (Jan. 4) 1936.

28. Girard, cited by Levaditi and Vaisman.[29a]

original German prontosil. The same year, Levaditi and Vaisman [29] confirmed the results of Domagk [11] concerning its bactericidal power for streptococci. Administered by mouth and intravenously, this drug was used by Vermelin and Hartemann [30] in the treatment of puerperal sepsis, and Floch [31] reported good results in the treatment of tropical streptococcic lymphangitis when the drug was administered by mouth. In studying its effects on the kidney damaged by acute hemorrhagic nephritis, Lemièrre, La Porte, Laudat and Daum [32] concluded the drug did not increase the existing renal impairment. Reporting its effects in 150 cases of erysipelas, Meyer-Heine [33] concluded that the chemical was a chemotherapeutic agent of great value. Bloch-Michel, Conte and Durel [34] reported favorable therapeutic effects in the treatment of erysipelas with paraaminobenzenesulfonamide (now known as sulfanilamide) and benzylparabenzenesulfonamide.

In England, Colebrook and Kenny,[12e] in 1936, first reported their experimental and clinical experience with the preparation of Girard (supposedly identical with the original prontosil) and with prontosil soluble. After preliminary experiments with mice, they utilized these drugs in the treatment of puerperal fever, observing not only a remarkable therapeutic effect but a definite decrease in the mortality of the patients so treated.

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29. Levaditi, C., and Vaisman, A.: (*a*) Action curative et préventive du chlorhydrate de 4′-sulfamido-2, 4-diamino-azobenzène dans l'infection streptococcique expérimentale, Compt. rend. Acad. d. sc. **200**:1694 (May 13) 1935; (*b*) Mecanisme de l'action curative et préventive du chlorhydrate de 4′-sulfamido-2,4-diaminoazobenzène et d'autres dérivés similaires dans l'infection streptococcique, expérimentale, Compt. rend. Soc. de biol. **120**:1077 (Dec.) 1935; (*c*) Action curative et préventive du chlorhydrate de 4′sulfamido-2,4-diaminoazobenzène et de quelques dérivés similaires dans la streptococcie expérimentale, Presse méd. **43**: 2097 (Dec. 25) 1935.

30. Vermelin, H., and Hartemann, D.: De l'emploi du chlorhydrate de sulfamidochrysoïdine en injections intraveineuses dans le traitement d l'I.P., Bull. Soc. d'obst. et de gynéc. **25**:158 (Feb.) 1936.

31. Floch, H.: Le traitement de la lymphangite endémique des pays chauds par le chlorhydrate de sulfamido-chrysoïdine, Bull. Soc. path. exot. **29**:165, 1936.

32. Lemièrre, A.; Laporte, A.; Laudat, M., and Daum, S.: Néphrite érysipélateuse. Action du bicarbonate de soude ingéré sur l'acidose. Innocuité du chlorhydrate de sulfamido-chrysoïdine pour le rein malade, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:535 (April 6) 1936.

33. Meyer-Heine, A., and Huguenin, P.: Traitement de l'érysipèle par le chlorhydrate de sulfamido-chrysoïdine, Presse méd. **44**:454 (March 18) 1936.

34. Bloch-Michel, H.; Conte, M., and Durel, P.: L'emploi des dérivés sulfamidés non azoïques dans le traitement de l'érysipèle, Presse méd. **44**:1583 (Oct. 10) 1936.

Schulte [2] stated that in 1935 the Tréfouëls, Nitti and Bovet,[35] collaborating with Fourneau,[36] recalled the hypothesis advanced in 1919 by Heidelberger and Jacobs.[10] They postulated that Girard's sulfonamidochrysoidine was broken down in the tissues to triaminobenzene and paraaminobenzenesulfonamide, which they assumed to be the pharmacologically effective portion of the prontosil molecule. Thus, paraaminobenzenesulfonamide (now known as sulfanilamide) was synthesized. In 1936, Goissedet, Despois, Gaillot and Mayer [37] synthesized parabenzylaminobenzenesulfonamide.

While many compounds related to the prontosils have been investigated, the work of Tréfouël and his coworkers [38] and of Buttle and his associates [39] during 1935 and 1936 indicated that paraaminobenzenesulfonamide, a part of the prontosil molecule, is the pharmacologically effective portion.[4] Sulfanilamide (paraaminobenzenesulfonamide) was stated to be more efficacious than its more complicated predecessors by Colebrook and Kenny [12e] in 1936 and Cooper, Gross and Mellon [40] in 1937. It was also established that sulfanilamide is formed from the prontosils by reduction in vivo.[41] Bliss and Long [41a] showed that the aminoacid cysteine produced an activation of prontosil soluble sufficient to be demonstrated in vitro as well as in vivo and that this activation was of a degree which would result were sulfanilamide formed.[4] Finally, Fuller [41b] isolated sulfanilamide from the urine of patients receiving

35. Tréfoulël, Tréfouël, Nitti and Bovet.[12a] Nitti and Bovet.[12c]

36. Fourneau, E., and others: (*a*) Chimiothérapie des infections streptococciques par les dérivés du p-aminophénylsulfamide, Compt. rend. Soc. de biol. **122**:258, 1936; (*b*) Action du para-aminophenylsulfamide sur les moisissures, ibid. **122**: 652, 1936; (*c*) Action antistreptococcique des dérivés sulfurés organiques, Compt. rend. Acad. d. sc. **204**:1763 (June 7) 1937.

37. Goissdet, P.; Despois, R.; Gaillot, P., and Mayer, R.: De l'action du radical sulfamide: SO_2NH_2 sur l'infection streptococcique expérimentale de la souris, Compt. rend. Soc. de biol. **121**:1082, 1936.

38. Tréfouël, Tréfouël, Nitti and Bovet.[12a] Nitti and Bovet.[12c] Fourneau and others (footnote 36 *a* and *b*).

39. (*a*) Buttle, G. A. H.; Gray, W. H., and Stephenson, D.: Protection of Mice Against Streptococcal and Other Infections by *p*-Aminobenzene-Sulphonamide and Related Substances, Lancet **1**:1286 (June 6) 1936. (*b*) Buttle, G. A. H., and others: Treatment of Streptococcal Infections in Mice with 4:4′ Diaminodiphenylsulphone, ibid. **1**:1331 (June 5) 1937. (*c*) Colebrook, L.; Buttle, G. A. H., and O'Meara, R. A. Q.: The Mode of Action of *p*-Aminobenzenesulfonamide and Prontosil in Haemolytic Streptococcal Infections, ibid. **2**:1323 (Dec. 5) 1936.

40. Cooper, F. B.; Gross, P., and Mellon, R. R.: Action of *p*-Aminobenzenesulfonamide on Type III Pneumococcus Infections in Mice, Proc. Soc. Exper. Biol. & Med. **36**:148 (March) 1937.

41. (*a*) Bliss, E. A., and Long, P. H.: Activation of "Prontosil Solution" in Vitro by Reduction with Cysteine Hydrochloride, Bull. Johns Hopkins Hosp. **60**:149 (Feb.) 1937. (*b*) Fuller, A. T.: Is *p*-Aminobenzenesulphonamide the Active Agent in Prontosil Therapy? Lancet **1**:194 (Jan. 23) 1937. (*c*) Colebrook, Buttle and O'Meara.[39c]

42-44. Footnotes deleted.

the original prontosil or prontosil soluble. These observations account for the fact that the prontosils have been shown to be essentially inactive in vitro.[4]

There is some evidence that the sulfonamide grouping is not essential to an action resembling that of sulfanilamide. Buttle and his associates [39b] investigated certain compounds related to sulfanilamide which do not contain the sulfonamide grouping. The streptococcicidal power of one of these, 4, 4′-diaminodibenzenesulfone, was claimed to be more active than that of sulfanilamide, but the drug is more toxic for mice. Another, 4, 4′-dinitrodibenzenesulfone, is less toxic than sulfanilamide but produces undesirable side effects. Fourneau, Tréfouël, Nitti, Bovet and Tréfouël [36c] have shown that 4, 4′-dinitrodibenzenesulfide and 4, 4′-dinitrodibenzenedisulfide have similar properties. These drugs are more efficacious when given by mouth than when injected subcutaneously. The sulfones produce symptoms which are more persistent than those produced by sulfanilamide.

Rosenthal, Bauer and Branham [45] concluded that disulfanilamide (sulfanilylsulfanilamide; paraaminobenzenesulfonylparaaminobenzenesulfonamide) was more effective than sulfanilamide in the treatment of streptococcic infections in mice and exhibited a toxicity one fifth of that of sulfanilamide. The maximum action of this drug, however, is obtained only by subcutaneous injection, owing to its low solubility and poor absorption from the gastrointestinal tract.

MODE OF ACTION

Although the mode of action of the prontosils on the streptococcus was not understood by the first German observers, Domagk [11] reported that phagocytosis of the streptococci by the leukocytes played an important role in clearing the tissues of streptococci in his treated mice. He noted also that such azo compounds had no effect on streptococci in vitro. Although Colebrook and Kenny [12e] found that Girard's sulfonamidochrysoidine and prontosil soluble when administered parenterally to normal human beings and to certain laboratory animals did not give the serum an inhibitory effect on streptococci in vitro, they found that the serum from patients ill with streptococcic infection did possess a definite bacteriostatic effect in vitro after the patients had been treated with one of these preparations.

Long and Bliss [46] were unable to confirm the observations on the serum of patients ill with streptococcic infections and attributed their

45. Rosenthal, S. M.; Bauer, H., and Branham, S. E.: Studies in Chemotherapy: IV. Comparative Studies of Sulphonamide Compounds in Experimental Pneumococcus, Streptococcus and Meningococcus Infections, Pub. Health Rep. **52**:662 (May 21) 1937.

46. Long, P. H., and Bliss, E. A.: (*a*) Para-Aminobenzenesulfonamide and Its Derivatives: Clinical Observations on Their Use in the Treatment of Infections Due to Beta Hemolytic Streptococci, Arch. Surg. **34**:351 (Feb.) 1937; (*b*) footnote 12 *f*.

results to the bactericidal property of the serums, a phenomenon described by Tillett.[47] Colebrook, Buttle and O'Meara [39e] demonstrated a bacteriostatic and bactericidal action of paraaminobenzenesulfonamide (sulfanilamide) against small numbers of hemolytic streptococci in culture mediums and in blood. They found the original prontosil and prontosil soluble to be inactive, as previously reported, but were able to demonstrate inhibitory effects when the original prontosil or prontosil soluble was reduced with magnesium powder in a partial vacuum. Other strong reducing agents, namely formaldehyde sulfoxylate [12f] and cysteine hydrochloride,[41a] were found by Long and Bliss to activate the inactive prontosil soluble as far as bacteriostasis was concerned. They [47a] observed also that large numbers of hemolytic streptococci had the power of partially reducing prontosil soluble in vitro. In advancing the hypothesis that in human patients ill with a streptococcic infection, a reduction of the prontosils to an active form is accomplished through an unknown reducing system, they pointed out that this hypothesis was based mainly on in vitro experiments and that the chemicals might prove to exert therapeutic effects in vivo which were not dependent on reduction to an active form. Long and Bliss [12f] suggested that the bacteriostatic action might not be an essential factor in the therapeutic results obtained.

Shortly after Domagk's original report, the Tréfouëls, Nitti and Bovet [12a] and later Buttle and his associates obtained indications that sulfanilamide (paraaminobenzenesulfonamide), a part of the prontosil molecule, is the pharmacologically effective portion. Colebrook and Kenny [12e] and Cooper, Gross and Mellon [40] reported sulfanilamide to be more efficacious than its more complicated predecessors. That sulfanilamide is formed from Girard's sulfonamidochrysoidine (supposedly identical with the original prontosil) and from prontosil soluble by reduction in vivo was established by Colebrook and Kenny,[12e] Bliss and Long [41a] and Fuller,[41b] and Bliss and Long demonstrated that the amino acid cysteine produced an activation of prontosil soluble sufficient to be demonstrated in vitro as well as in vivo and comparable to that to be expected were sulfanilamide formed. Finally, Fuller [41b] was able to isolate sulfanilamide from the urine of patients treated with the original prontosil or with prontosil soluble.

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47. Tillett, W. S.: The Bactericidal Action of Human Serum on Hemolytic Streptococci: Observations Made with Serum from Patients with Acute Infections and from Normal Individuals, J. Exper. Med. **65**:147 and 163 (Jan.) 1937.

47a. Long, P. H., and Bliss, E. A.: Use of Sulfanilamide or Derivatives in Treatment of Infections Due to Beta Hemolytic Streptococci, South. M. J. **30**:479 (May) 1937.

Colebrook and his associates [39c] suggested that the bactericidal action of the tissues of the whole animal might be important in obtaining the effects of the drug, but Long and Bliss [12f] were inclined to believe that the phagocytic activity of the polymorphonuclear leukocytes and monocytes played a paramount role in controlling infections caused by beta hemolytic streptococci. Gross, Cooper and Peebles,[48] by experiments with mice, were unable to demonstrate a greater indication of phagocytosis in treated animals than in the untreated controls. Weinberg, Mellon and Shinn [49] found no indications of increased phagocytosis in animals treated with sulfanilamide.

Levaditi and Vaisman [12b] had early suggested that the drug acted by preventing the formation of capsules. Various authors theorized on the possible role of the reticuloendothelial system, which might combat streptococcic infections when stimulated by the sulfonamide compounds. Bosse [50] claimed to have demonstrated a considerable weakening of the protective action of prontosil (preparation not specified) against hemolytic streptococcic infections in splenectomized mice but gave no details regarding the number of mice employed or the manner in which the experiment was controlled. A possible role of the reticuloendothelial system appears to have been eliminated by the finding of Gross, Cooper and Peebles [48] that sulfanilamide is capable of protecting splenectomized mice against fatal doses of highly virulent hemolytic streptococci and that the degree of protection observed in splenectomized mice was identical with that obtained with normal animals.

Levaditi and Vaisman [29b] demonstrated the neutralizing effect of sulfanilamide and various derivatives on the leukocidins and hemolysins of streptococci in vitro. Rosenthal,[51] in reporting that sulfanilamide was bactericidal for pneumococci, emphasized that the drug is more effective against streptococci than against pneumococci in animals but is not inhibitory to the growth of streptococci in the test tube. The bacteriostatic and bactericidal action of sulfanilamide on pneumococci in vitro was regarded by Rosenthal as adequate explanation for its chemotherapeutic effect in animals. The nature of this action in vitro is unusual, since the drug is not an antiseptic in the usual sense.

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48. Gross, P.; Cooper, F. B., and Peebles, M. L.: Effect of Splenectomy on the Therapeutic Action of *p*-Aminobenzenesulfonamide on Mice Infected with Hemolytic Streptococcus, Proc. Soc. Exper. Biol. & Med. **36**:311 (April) 1937.

49. Weinberg, M. H.; Mellon, R. R., and Shinn, L. E.: Two Cases of Streptococcic Meningitis Treated Successfully with Sulfanilamide and Prontosil, J. A. M. A. **108**:1948 (June 5) 1937.

50. Bosse, O. A.: Die Therapie der Streptokokkenerkrankungen mit "Prontosil," Fortschr. d. Therap. **12**:540 (Sept.) 1936.

51. Rosenthal, S. M.: Studies in Chemotherapy: III. The Effect of *p*-Aminobenzene Sulphonamide on Pneumococci in Vitro, Pub. Health Rep. **52**:192 (Feb. 12) 1937.

Hawking [52] reported that 1:1,000 solutions of sulfanilamide had no effect on the intestine of the rabbit or uterus of the guinea pig suspended in vitro at 37 C. or on the heart of the frog perfused through the inferior vena cava. No effect on the blood pressure in the cat or dog occurred when 0.17 Gm. of the drug per kilogram of body weight was given. Intraperitoneal injections of large doses in animals caused no local irritation. Large doses, of 1.5 to 2 Gm. per kilogram of body weight, occasionally produced death in rabbits and cats. Weakness of the legs, dyspnea, panting, general appearance of decerebrate rigidity and the like were commonly noted. The surviving animals were killed after a week, but the liver, kidneys and viscera showed no changes histologically. In 3 animals dying of the effects of drug, degenerative changes (chromatolysis) were observed in the neurons of the anterior column of the spinal cord and in some of the neural cells of the cortex and midbrain.

Gay and Clark [53] found that the serum, defibrinated blood and artificial pleural exudate of rabbits treated with sulfanilamide inhibit the growth of streptococci in vitro but that repeated doses of such treated serum fail to sterilize the culture. The coccic chains grown in serum so treated are elongated and present pleomorphic and metachromatic organisms and may give rise to colonies that are at first less predominantly mucoid in appearance. Such organisms have lost little if any of their virulence. Cooperation on the part of locally derived clasmatocytes is apparently required for complete sterilization of the animal body. Sulfanilamide produces bacteriostasis sufficiently marked to protect the accumulated leukocytes and to allow the natural accumulation of defensive macrophages. There is no direct evidence that the drug does not in itself stimulate the mobilization of the macrophages, according to Gay and Clark, and they feel there is no evidence that the reaction in the cells which finally accounts for the disposal of the organisms is other than local.

Bliss and Long [54] attempted to determine whether or not the presence of polymorphonuclear leukocytes is a necessary adjunct to sulfanilamide therapy. Mice were rendered granulocytopenic by the administration of benzene. As controls for each granulocytopenic mouse infected with virulent hemolytic streptococci and treated with sulfanilamide, similarly infected mice were employed, consisting of a normal mouse, an untreated

52. Hawking, F.: Pharmacological Actions of Sulphanilamide, Lancet **2**:1019 (Oct. 30) 1937.

53. Gay, F. P., and Clark, A. R.: On the Mode of Action of Sulfanilamide in Experimental Streptococcus Empyema, J. Exper. Med. **66**:535 (Nov.) 1937.

54. Bliss, E. A., and Long, P. H.: Observations on the Mode of Action of Sulfanilamide, J. A. M. A. **109**:1524 (Nov. 6) 1937.

granulocytopenic mouse, a mouse treated with benezene and sulfanilamide, a mouse treated with benzene, and a mouse treated with sulfanilamide. The untreated control mice died within thirty-six hours, the untreated granulocytopenic mice within twenty-four hours, the mice treated with benzene within thirty-six hours and the granulocytopenic mice treated with sulfanilamide within seventy-two hours, while the mice treated with sulfanilamide and those treated with benzene and sulfanilamide survived. The experiment seems to prove that polymorphonuclear leukocytes are necessary in the process that leads to control of infection in mice treated with sulfanilamide.

Further experiments with experimental streptococcic infections in mice led Bliss and Long [54] to believe that the action of sulfanilamide is primarily one of slowing down the rate of multiplication of the streptococci and thus permitting the phagocytes to dispose of them before they exert a lethal effect on the mouse. They failed to demonstrate alteration in the hemolytic streptococci isolated from the peritoneal exudates of treated infected mice in so far as type of colonial formation, virulence for mice or presence of capsular material were concerned; in these respects the streptococci were identical with those isolated from untreated control mice. Bliss and Long also observed that when peritonitis is experimentally induced in mice by infection with Welch's bacillus death quickly occurs in untreated mice from overwhelming toxemia. The organism itself is not resistant to phagocytosis, and from the beginning of infection the phagocytes are filled with ingested bacteria. When a lethal dose is injected, however, the leukocytes, although extraordinarily active in phagocytosis, cannot ingest enough bacteria to keep pace with the multiplication of, and formation of toxin by, the organism, and the mouse succumbs in a short time. Up to the time of death there is no evidence that phagocytosis is either absolutely or relatively decreased in the untreated mice. This sequence of events was definitely altered when treatment with sulfanilamide was instituted. From the very beginning of treatment, there was a decrease in the number of free bacilli in the peritoneal exudate. Phagocytosis was marked, but the total number of ingested bacteria in the case of the treated mice was less than in the case of the control mice. Successive observations showed a progressive decrease in the number of free and ingested bacteria in the peritoneal exudates. Bliss and Long expressed the opinion that, since the only essential difference between the untreated and the treated mice was in the number of bacteria free in the exudates at the various periods of observation, the only interpretation of the facts was that sulfanilamide inhibited the growth of the bacteria in vivo. They concluded from their experiments with streptococcic peritonitis in mice that the action of sulfanilamide was that of bacteriostasis rather

than that of a direct protective or stimulative action on the phagocytes; it appeared that in this type of infection the effect of the sulfanilamide therapy is to reduce the rate of multiplication of the streptococci to a point at which they no longer produce enough leukocidin and other toxic products to inhibit rapid phagocytosis. This effect permits the exudates and tissues to be freed of organisms by the leukocytes, and recovery from infection follows.

Turning to marrow cultures for the study of the effects of sulfanilamide on living human marrow cells, Osgood and Brownlee [55] were able to throw further light on the mechanism involved in the control of infection with hemolytic streptococci by this drug. Cultures of living human marrow cells containing sulfanilamide in concentrations of 1 : 250 to 1 : 500,000 did not differ from control cultures without sulfanilamide for the first forty-eight hours in cell count, number of mitotic figures, structure of cells, differential count, appearance with supravital stains or ability to phagocytose bacteria. On exposure for a period of eight days or less, concentrations of sulfanilamide of less than 1 : 1,000 did not grossly affect the growth of the marrow cells. Marrow cultures infected with hemolytic streptococci and containing sulfanilamide in concentrations of 1 : 100,000 or more were sterile in subculture and contained no visible streptococci in stained smears after twenty-four hours; infected controls showed gross hemolysis and complete destruction of all leukocytes and erythrocytes. Osgood and Brownlee noted no variation in the effectiveness of concentrations of sulfanilamide from 1 : 1,000 to 1 : 100,000; even a concentration of 1 : 6,000,000 showed an appreciable bacteriostatic action.

Cultures of hemolytic streptococci in Hartley's broth appeared grossly sterile after twenty-four hours in the presence of sulfanilamide in concentrations of 1 : 1,000 to 1 : 100,000, but all the tubes became turbid in from forty-eight to seventy-two hours. Osgood and Brownlee felt that this indicated a definite effect of sulfanilamide on the growth of beta hemolytic streptococci in the absence of human serum or marrow cells but emphasized the fact that the cultures did not become sterile. They demonstrated that the failure of sulfanilamide to kill streptococci in all instances was not due to the development of a resistant strain and that destruction of sulfanilamide does not explain the survival of large inoculations of streptococci. Osgood and Brownlee [55] stated that the major action of sulfanilamide on infections with beta hemolytic streptococci is the neutralization or destruction of toxins and the decrease in the rate of division of the organisms and concluded that the bacteriocidal

55. Osgood, E. E., and Brownlee, I. E.: Culture of Human Marrow: Studies on the Mode of Action of Sulfanilamide, J. A. M. A. **110**:349 (Jan. 29) 1938.

action of human serum and the phagocytic action of the neutrophils and monocytes of the marrow and blood overcome the infection not because sulfanilamide kills the streptococci but because it neutralizes the toxins and decreases the rate of multiplication.

In the light of these experiments it appears that sulfanilamide in concentrations of 1 : 100,000 may be effective, and this may explain the fact that a number of compounds [56] which are not in themselves bacteriostatic but which break down in the body to yield sulfanilamide become effective in doses insufficient to form sulfanilamide in concentrations of 1 : 10,000 in the blood. Colebrook, Buttle and O'Meara [39c] had observed a discrepancy between the failure to kill streptococci with a 1 : 100 solution of sulfanilamide in broth and the killing of streptococci with much lower concentrations in blood, attributing this to a bactericidal or bacteriostatic action of sulfanilamide. They noted that in monkeys twenty-four hours after administration of sulfanilamide the blood was still capable of overcoming an infection with an inoculation of 6,000 streptococci per cubic centimeter. The concentration of sulfanilamide in the blood at this time, as shown by Marshall, Emerson and Cutting's data on excretion,[57] was probably much less than 1 : 10,000.

Of practical clinical importance are the following conclusions of Osgood and Brownlee.[55] The continuous presence of a low concentration of sulfanilamide is more effective than the intermittent presence of a high concentration. The smaller the number of organisms, the greater is the effectiveness of the drug, and therefore therapy should be instituted at the earliest possible moment. Small doses at frequent intervals to maintain the concentration of the drug in the body fluids above 1 : 100,000 at all times are more effective than large doses at longer intervals. Therapy should not be discontinued until cultures are negative; if viable organisms remain, recrudescence is almost inevitable, and the administration of the drug must be resumed.

Hemmens and Dack,[58] however, stated that the results of Osgood and Brownlee, Colebrook, Buttle and O'Meara and Long and Bliss

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56. (*a*) Gley, P., and Girard, A.: Un nouveau dérive de la sulfamidochrysoïdine très actif contre l'infection streptococcique, Presse méd. **44**:1775 (Nov. 11) 1936. (*b*) Tréfouël, J.; Tréfouël, J. (Mme.); Nitti, F., and Bovet, D.: Chimiothérapie des infections streptococciques par les dérivés du p-aminophénylsulfamide, Ann. Inst. Pasteur **58**:30 (Jan.) 1937. (*c*) Bovet, D.: Recherches expérimentales dans le domaine de la chimiothérapie des infections bactériennes, Schweiz. med. Wchnschr. **67**:288 (April 3) 1937. (*d*) Levaditi and Vaisman.[29c] (*e*) Fourneau and others.[36c]

57. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Para-Aminobenzenesulfonamide: Absorption and Excretion; Method of Determination in Urine and Blood, J. A. M. A. **108**:953 (March 20) 1937.

58. Hemmens, E. S., and Dack, G. M.: Mode of Action of Sulfanilamide, J. A. M. A. **110**:1209 (April 9) 1938.

could be adequately explained by an inhibitory action of the drug on the reproductive rate of the organism and that it seems unnecessary to postulate any direct effect of the drug on the toxins of beta hemolytic streptococci in order to explain this action, especially since a bacteriostatic action of the drug was not excluded by their experiments. Slowing of the metabolism of the organisms, reflected by a slower rate of reproduction, also might account for diminished production of toxic substances, and Hemmens and Dack noted that such an action would explain their observation of some decrease in the size of hemolyzed areas about colonies produced by organisms which had been exposed to sulfanilamide. They also found that a non-toxin-producing organism, Bacillus necrophorus, invariably produced fatal disease in rabbits when a virulent bovine strain was used. The infection, however, could be controlled and cured by treating the infected animals with sulfanilamide. If this observation is substantiated, it would negate the thesis that the elaboration of an exotoxin by an organism is necessary to the action of sulfanilamide against that organism.

Finklestone-Sayliss, Paine and Patrick [59] concluded that sulfanilamide does not modify the activities of the polymorphonuclear leukocytes but found that the drug stimulated the phagocytic activity of the reticuloendothelial cells of rabbits. The effect of sulfanilamide on the leukocytes has received much attention.[60] Bigler, Clifton and Werner [61] administered the drug by mouth on the basis of 15 grains (1 Gm.) to 20 pounds (9 Kg.) of body weight, irrespective of age. In patients with leukocytosis, the white cell count tended to drop within twenty-four to thirty-six hours after clinical improvement was noted, although occasionally the drop occurred forty-eight or more hours after clinical improvement. In some instances, the leukocytosis was unchanged, and in long drawn out infections the leukocyte count could not be lowered. In no instance did the authors note during the administration of sulfanilamide an increase in the white cell count which was not attributable to the infection. Leukopenia was likely to occur in patients with a normal leukocyte count when sulfanilamide was administered. That the drug caused a depression of leukocytes was evidenced by the production of leukopenia and the rapid fall of leukocytes at the end of an infection, often followed by a moderate increase in leukocytes after the drug was

59. Finklestone-Sayliss, H.; Paine, C. G., and Patrick, L. B.: Bacteriostatic Action of *p*-Aminobenzenesulfonamide upon Hemolytic Streptococci, Lancet **2**: 792 (Oct. 2) 1937.

60. Sulfanilamide and the Leukocytes, editorial, J. A. M. A. **110**:372 (Jan. 29) 1938.

61. Bigler, J. A.; Clifton, W. M., and Werner, M.: The Leukocyte Response to Sulfanilamide Therapy, J. A. M. A. **110**:343 (Jan. 29) 1938.

discontinued. The alteration in leukocyte response [61] appears to be a marked absolute reduction of all the cell elements without characteristic relative change; the granulocytes are not reduced out of proportion to the other cells. The Schilling differential count merely reflects what may be considered a healing infection.[61] Bigler, Clifton and Werner [61] noted little effect on either red blood cells or platelets and could find little if any fall in the hemoglobin content of the blood.

Hawking [52] found that sulfanilamide has almost no action on the smooth muscles, the heart or the blood pressure. When large doses were given to rabbits or cats, it produced nervous symptoms somewhat resembling decerebral rigidity. In normal animals [41b] 35 per cent of ingested sulfanilamide and 49 per cent of prontosil soluble were not accounted for. In infected animals 54 per cent of the ingested sulfanilamide and 61 per cent of prontosil soluble were not accounted for. This may be due to retention by the inflamed tissues or to impairment of kidney function. Czarnetzky and Sevag [62] have recently pointed out the possibility that inorganic sulfites might be substituted for sulfanilamide in the chemotherapy of streptococcic infection.

As shown by Marshall, Emerson and Cutting,[57] sulfanilamide is approximately equally distributed in the tissues of the organism (with the exception of bone and fat) and is probably present in equal concentration in all parts of the body if the concentrations are expressed per unit of water. Earlier observers had become convinced that sulfanilamide when administered by mouth was almost completely absorbed from the gastrointestinal tract in about four hours. The drug appears to pass readily from the blood stream and to become widely distributed throughout the tissues, in which the concentration is only slightly lower than in the blood. Simultaneous determinations of sulfanilamide in the blood and in the spinal fluid of man [63] during several hours of administration of the drug indicated that the concentration in the spinal fluid is parallel to and only slightly lower than that in the blood. The presence of the drug has been demonstrated in the saliva, the urine, the pancreatic juice, the bile, the cerebrospinal fluid, the blood plasma and the nasal and the lacrimal secretion.

While Temming [64] first used the original prontosil in the treatment of urinary infections, its successful use in the urinary infections of

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62. Czarnetzky, E. J., and Sevag, M. G.: The Action of Sodium Bisulphite and Sulfanilamide on Purine and Pyrimadine Compounds with the Production of Hemolysins, and a Suggested Mechanism of the Action of Sulfanilamide on Hemolytic Streptococci, Am. J. M. Sc. **195**:426 (March) 1938.

63. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: The Distribution of Sulfanilamide in the Organism, J. Pharmacol. & Exper. Therap. **61**:191 (Oct.) 1937.

64. Temming, C. E., cited by Maraun.[65d]

childhood was soon reported by numerous other clinicians.[65] The effectiveness of sulfanilamide in the treatment of urinary infections demonstrated by other investigators [66] stimulated a study of the renal excretion of the drug. Marshall, Emerson and Cutting [57] and Fuller [41b] demonstrated that sulfanilamide is partially converted in man and in the rabbit into a conjugated form. Thus, the drug is practically entirely excreted in the urine in a free state and in the conjugated form as paraacetylaminobenzenesulfonamide. Harris and Klein [67] in experiments with tissue (liver, muscle, spleen, kidney and blood) concluded that only the liver could convert sulfanilamide into the conjugated form. Marshall, Emerson and Cutting [63] demonstrated that the clearance of sulfanilamide in the urine is independent of the plasma level and is increased by an increase in the rate of flow of the urine. Helmholz, and Osterberg [66d] found that sulfanilamide given by mouth produces a urine strongly bactericidal for organisms usually found in infections of the urinary tract with the exception of Streptococcus faecalis. They found the same concentration of the drug more bactericidal in alkaline than in acid urine and later reported [68] that sulfanilamide in its free form when added in concentrations of only 25 to 40 mg. of sulfanilamide per hundred

65. (*a*) Unshelm, E.: Zur Behandlung der kindlichen Pyurie, Arch. f. Kinderh. **109**:65, 1936. (*b*) Helmholz, H. F.: Use of Sulfanilamide as Urinary Antiseptic, J. Pediat. **11**:243 (Aug.) 1937. (*c*) Klein, E.: Prontosil in der Kinderpraxis, Med. Klin. **33**:940 (July 10) 1937. (*d*) Maraun, L.: Zur Prontosilbehandlung des Erysipels und der Pyurie, Kinderärztl. Praxis **7**:445 (Oct.) 1936. (*e*) Pernice, W.: Ueber der Behandlung der kindlichen Pyurie mit Prontosil, ibid. **7**:304 (July) 1936.

66. (*a*) Cook, E. N., and Buchtel, H. A.: The Use of Sulfanilamide (Prontylin) in Urinary Infections, Proc. Staff Meet., Mayo Clin. **12**:381 (June 16) 1937. (*b*) Buchtel, H. A., and Cook, E. N.: The Use of Sulfanilamide (Prontylin) in Urinary Infections, ibid. **12**:433 (July 14) 1937. (*c*) Helmholz, H. F.: Comparison of Mandelic Acid and Sulfanilamide as Urinary Antiseptics, J. A. M. A. **109**:1039 (Sept. 25) 1937. (*d*) Helmholz, H. F., and Osterberg, A. E.: Rate of Excretion and Bactericidal Power of Sulfanilamide in Urine, Proc. Staff Meet., Mayo Clin. **12**:377 (June 16) 1937. (*e*) Barer, M.: Typhoid Bacilluria Treated with Sulphanilamide, Lancet **2**:964 (Oct. 23) 1937. (*f*) Helmholz, H. F.: Bactericidal Power of the Urine After the Administration of Prontylin by Mouth, Proc. Staff Meet., Mayo Clin. **12**:244 (April 21) 1937. (*g*) Dees, J. E., and Colston, J. A. C.: The Use of Sulfanilamide in Gonococcic Infections, J. A. M. A. **108**:1855 (May 29) 1937. (*h*) Walther, H. W. E.: Urinary Antisepsis: Historical Review and Present Evaluation, ibid. **109**:999 (Sept. 25) 1937. (*i*) Hoerlein, H.: Development of Chemotherapy for Bacterial Diseases, Practitioner **139**:635 (Dec.) 1937.

67. Harris, J. S., and Klein, J. R.: Acetylation of Sulfanilamide by Liver Tissue in Vitro, Proc. Soc. Exper. Biol. & Med. **38**:78 (Feb.) 1938.

68. Helmholz, H. F., and Osterberg, A. E.: The Effect of p_H of the Urine on Concentration of Free and Conjugated Sulfanilamide Necessary for Bactericidal Action, Proc. Staff Meet., Mayo Clin. **12**:661 (Oct. 20) 1937.

cubic centimeters to an alkaline urine acts bactericidally. Concentrations as low as 25 to 30 mg. per hundred cubic centimeters when excreted in alkaline urine act bactericidally.

The determination of sulfanilamide in biologic mediums was stimulated by the detection of the drug in the urine and the blood. Marshall and his coworkers,[69] Kellner [70] and Scudi [71] contributed to the advance in the technic of identifying the drug in tissues and secretions. Marshall and Babbitt [72] reported a method for the determination of sulfanilamide in blood and urine based on the diazotization of the para-aminobenzenesulfonamide with nitrous acid and the coupling of the resulting diazo compound in acid solution with dimethyl-α-naphthylamine to produce a purplish red azo dye which can be easily estimated by colorimetric comparison.

EFFECT ON EXPERIMENTAL INFECTIONS IN ANIMALS

Although Domagk [11] demonstrated in 1935 that the original prontosil in doses one tenth to one fiftieth of the tolerated amount, given over a period of three to five days, protected mice against ten times the lethal dose of hemolytic streptococci, the Tréfouëls, Nitti and Bovet [12a] were the first to show the activity of sulfanilamide in streptococcic infections of mice. Mice inoculated intraperitoneally with a strain of hemolytic streptococcus isolated in a case of fatal septicemia were treated with the hydrochloride of paraaminobenzenesulfonamide by mouth for two days; the treated mice survived in some instances for more than ten days, while the control mice died in less than forty-eight hours. Rabbits inoculated with a virulent strain of hemolytic streptococcus when given the drug by mouth survived from two days to one week longer than the controls. Goissedet and his coworkers [37] confirmed the finding that the antistreptococcic power may exist in a molecule possessing the sulfonamide and amino radicals but not the azo group.

It was soon noted that prolonged survival of all the animals treated was rare regardless of the manner in which the drug was administered.[73]

69. Marshall, E. K., Jr.: Determination of Sulfanilamide in Blood and Urine, Proc. Soc. Exper. Biol. & Med. **36**:422 (April) 1937. Marshall, E. K., Jr.; Cutting, W. C., and Emerson, K., Jr.: Acetylation of Para-Amino-Benzene-Sulfonamide in the Animal Organism, Science **85**:202 (Feb. 19) 1937. Footnotes 57 and 63.

70. Kellner, K.: Etude sur l'élimination de la sulfamido-chrysoïdine, Thesis, Paris, no. 652, 1936.

71. Scudi, J. V.: Determination of Sulfanilamide in Biologic Mediums, J. Biol. Chem. **122**:539 (Jan.) 1938.

72. Marshall, E. K., Jr., and Babbitt, D.: Determination of Sulfanilamide in Blood and Urine, J. Biol. Chem. **122**:263 (Dec.) 1937.

73. Holman, W. L., and Duff, G. L.: Sulfanilamide and Similar Compounds in Chemotherapy, Am. J. M. Sc. **195**:379 (March) 1938.

Living cocci were frequently obtained from the blood or tissues of treated mice long after the untreated controls had died.[73] Furthermore, animals dying after long periods of streptococcic infection frequently failed to show the pathologic lesions characteristic of death from streptococci. These observations were contrary to the conception of a germicidal or antiseptic action on the part of the drug. Buttle and his associates [39] and Proom [74] confirmed the work of the Tréfouëls and further showed that the treatment with sulfanilamide of mice infected with hemolytic streptococci and meningococci was more effective than that with the original prontosil.[75] Standardization of experimental procedures with sulfanilamide in animals was advanced by Buttle [39a] and Whitby.[76]

Colebrook and Kenny [77] in observing the therapeutic effect of sulfanilamide on streptococcic septicemia of mice found that with a single exception all the controls died after forty-eight hours, while the treated animals survived for more than thirty days and only 1 died on the thirty-second day. The surviving treated mice were killed on the thirty-fourth and the thirty-fifth day, and the cultures of the blood were found sterile. While intraperitoneal injections of hemolytic streptococci have been employed in most of the experimental work, other sites of injection have been employed. Berger and Schnetz [78] produced streptococcic abscesses in mice by subcutaneous injection of the organisms. Administration of prontosil soluble by mouth five hours later with the dose repeated up to five days prevented the general spread of infection and the establishment of fatal metastases in a majority of mice. Long and Bliss [12f] observed a marked reduction in the growth of hemolytic streptococci when various concentrations of sulfanilamide were used in broth culture as well as in the presence of 50 per cent normal horse serum broth. They [46a] noted that some mice, however, died thirty-nine days and even sixty-three to one hundred and twenty-eight days after treatment was discontinued, although apparently in good health during the interval. Levaditi and Vaisman [12b] reported mice dying of hemolytic streptococcic infection eighteen to nineteen days after apparent cure.

74. Proom, H.: Therapeutic Action of *p*-Aminobenzenesulphonamide in Meningococcal Infection of Mice, Lancet **1**:16 (Jan. 2) 1937.

75. Buttle, G. A. H.: Chemotherapy in Streptococcic Infections, J. A. M. A. **108**:747 (Feb. 27) 1937.

76. Whitby, L. E. H.: (*a*) Assessment of Efficiency of Chemotherapeutic Substances, Practitioner **139**:650 (Dec.) 1937; (*b*) An Experimental Assessment of the Therapeutic Efficacy of Amino Compounds with Special Reference to *p*-Benzylaminobenzenesulfonamide, Lancet **1**:1517 (June 26) 1937.

77. Colebrook, L., and Kenny, M.: (*a*) Treatment with Prontosil of Puerperal Infections Due to Hemolytic Streptococci, Lancet **2**:1319 (Dec. 5) 1936; (*b*) footnote 12 *e*.

78. Berger, W., and Schnetz, H.: Ein Behandlungserfolg bei Morbus Bang mit Prontosil, Med. Klin. **33**:594 (April 30) 1937.

Raiziss, Severac and Moetsch [79] investigated the toxicity of sulfanilamide by using the drug subcutaneously in mice, intravenously in rats and rabbits and orally in rabbits. The maximum tolerated dose (administered subcutaneously) for mice was found to lie between 2 and 2.5 Gm. per kilogram of body weight. The maximum tolerated dose (administered intravenously) for rabbits and rats could not be determined because of the limited solubility of sulfanilamide, but rats tolerated 0.4 Gm. per kilogram of body weight and rabbits 0.2 Gm. Oral administration of sulfanilamide in doses of 2 Gm. per kilogram of body weight was fatal in 50 per cent of rabbits; 2.5 Gm. was lethal, but 1.5 Gm. was tolerated by 94 per cent of rabbits. The investigators concluded that one-fourth the maximum tolerated dose is necessary to produce a curative effect in mice infected with a very virulent strain of beta hemolytic streptococci. Rosenthal [79a] found that no symptoms were produced when sulfanilamide was administered to mice in doses of 1 Gm. per kilogram of body weight twice a day for two days, followed by 0.5 Gm. per kilogram twice a day for three days. A 50 per cent increase of the dose over similar periods produced loss of weight but no deaths. A mortality of 50 per cent occurred when an increase to 2 Gm. per kilogram was employed in the first period and to 1 Gm. per kilogram in the second period.

The work of Gay and Clark [53] has been previously described as demonstrating the effectiveness of sulfanilamide in experimental empyema in the rabbit. Kolmer, Brown and Raiziss [80] reported the therapeutic effect of sulfanilamide in experimental infections of the skin and the joints in rabbits. Numerous workers [81] became concerned with

79. Raiziss, G. W.; Severac, M., and Moetsch, J. C.: Chemotherapeutic Studies of Sulfamidyl (Para-Amino-Benzene-Sulfonamide) in Experimental Beta-Hemolytic Streptococcic Infection, J. Chemotherapy **14**:1 (April) 1937.

79a. Rosenthal, S. M.: Studies in Chemotherapy: II. Chemotherapy of Experimental Pneumococcus Infections, Pub. Health Rep. **52**:48 (Jan. 8) 1937.

80. Kolmer, J. A.; Brown, H., and Raiziss, G. W.: Chemotherapy of Experimental Streptococcus Infections of Rabbits with Special Reference to Pyridine Compounds and Prontosil Soluble, J. Pharmacol. & Exper. Therap. **61**:253 (Nov.) 1937.

81. (*a*) Schwentker, F. F., and others: Use of Para-Amino-Benzene-Sulphonamide or Its Derivatives in Treatment of Beta Hemolytic Streptococcic Meningitis, Bull. Johns Hopkins Hosp. **60**:297 (April) 1937. (*b*) Girard, A.; Ray, A., and Richard, G.: Antimicrobial Action of Some Aromatic Compounds, Nature, London **140**:283 (Aug. 14) 1937. (*c*) Nitti, F., and Bovet, D.: La chimiothérapie des infections microbiennes et les nouveaux essais de traitement et de prévention des streptococcies, Rev. d'immunol. **2**:450, 1936; (*d*) Les septicémies streptococciques expérimentales et leur traitement par le *p*-amino-phenylsulfamide, Compt. rend. Acad. d. sc. **202**:1221, 1936. (*e*) Gray, W. H.; Buttle, G. A. H., and Stephenson, D.: Derivatives of *p*-Aminobenzenesulfonamide in the Treatment of Streptococcal Infection in Mice, Biochem. J. **31**:724 (May) 1937. (*f*) Chemo-

(Footnote continued on next page)

investigations of streptococcic infections in animals and the response to sulfanilamide therapy. While the beta hemolytic streptococcus was found particularly susceptible to the sulfanilamide group of compounds, the streptococci of the Lancefield group A were thought to be almost exclusively susceptible. Long and Bliss [82] found that the Lancefield groups A and B were susceptible to sulfanilamide but noted that the drug was ineffective against the Lancefield group D beta hemolytic streptococci. Seastone [83] found that guinea pigs inoculated with Lancefield's group C hemolytic streptococci were protected by adequate doses of sulfanilamide.

Finklestone-Sayliss, Paine and Patrick [59] found that the bacteriostatic action of sulfanilamide on hemolytic streptococci is preceded by a phase of stimulation of growth. This stimulation is more conspicuous in young cultures than in cultures that have passed through the logarithmic phase of growth. They found also that sulfanilamide is more soluble in the fatty envelop which can be separated from hemolytic streptococci than in aqueous solution. Sulfanilamide has consistently failed to be effective against alpha hemolytic streptococci (Streptococcus viridans). Welch [4] considers this noteworthy since it has been established that neoarsphenamine, which has a demonstrable action on certain streptococci in blood, is also without effect on Str. viridans.

While clinical use of sulfanilamide in staphylococcic infections has had disappointing results, Domagk [11] obtained favorable results in acute spreading infections in rabbits, and the first mention of the sulfanilamide group of drugs in medical literature was that of Foerster,[13] who reported that prontosil soluble (streptozon) had shown a marked chemotherapeutic effect on a boy suffering from a generalized staphylococcic infection. Helmholz [66c] showed that sulfanilamide in concentrations easily obtainable by oral administration rendered the urine bactericidal for Staphylococcus aureus.

The effect of sulfanilamide on pneumococcic infections has received much attention, but in general the experimental results in animals have been better than the results of the clinical application of the drug in

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therapy in Streptococcic Infections, editorial, J. A. M. A. **108**:48 (Jan. 2) 1937. (*g*) Peters, B. A., and Havard, R. V.: Chemotherapy of Streptococcal Infections with *p*-Benzylamino-Benzene-Sulfonamide, Lancet **1**:1273 (May 29) 1937. (*h*) De, S. P., and Basu, U. P.: Action of *p*-Amino Benzene Sulphonamide Against Streptococcic Infections in Mice, Indian J. M. Research **25**:465 (Oct.) 1937. (*i*) Buttle and others.[39b]

82. Bliss, E. A., and Long, P. H.: Failure of Para-Aminobenzenesulfonamide Therapy in Urinary Tract Infections Due to Group D (Lancefield) Beta Hemolytic Streptococci, New England J. Med. **217**:1 (July 1) 1937.

83. Seastone, C. V.: Effect of Sulfanilamide on Group C Hemolytic Streptococcic Infections, J. Immunol. **33**:403 (Nov.) 1937.

man. Domagk [84] had reported the partial effectiveness of the original prontosil and prontosil soluble on the type III pneumococcus but regarded the drugs as of little value in treating infection caused by type I and type II pneumococci. He later [85] found sulfanilamide more effective in pneumococcic infections than the original prontosil, and this opinion was supported by Colebrook and Kenny [77a] and Cooper, Gross and Mellon.[40] Hörlein,[85a] in reviewing Domagk's work, asserted that the compound was effective against infections with type III pneumococci but failed to publish in detail his experimental results leading to this conclusion. Rosenthal [86] showed that sulfanilamide used therapeutically prolonged the lives of mice infected with ten to one hundred times the minimum lethal dose of types I, II and III pneumococci. Cooper, Gross and Mellon,[40] independently, made a similar finding concerning infections with type III pneumococci but noted that the drug was not as effective in its action as in the case of streptococcic and meningococcic infections. They felt that their experiments, however, justified the use of the drug in treating human beings infected with type III pneumococci. Nitti, Bovet and Depierre [87] found a direct inhibitory action of sulfanilamide on pneumococci in vitro. Buttle, Parish, McLeod and Stephenson [88] were unable to demonstrate any significant protective action on mice infected with pneumococci of types I and II, whereas Rosenthal [79a] obtained protection for experimental animals against all three fixed types.

Gross and Cooper [90] recalled the lack of parallelism between pneumococcic septicemia in mice and pneumonia in man, and this led to the choice of experimental pneumococcic pneumonia in rats as a closer approximation to human pneumonia. Rats were infected intra-

84. Domagk, G.: Chemotherapie der bakteriellen Infektionen, Jahrb. d. angew. Chem. **48**:657, 1935; Chemotherapie die Streptokokken-Infektionen, Klin. Wchnschr. **15**:1585 (Oct. 31) 1936; footnote 11.

85. Domagk, G.: Weitere Untersuchungen über die chemotherapeutische Wirkung sulfonamidhaltiger Verbindung bei bacteriellen Infektionen, Klin. Wchnschr. **16**:1412 (Oct. 9) 1937.

85a. Hörlein, H.: Chemotherapy of Infectious Diseases Caused by Protozoa and Bacteria, Proc. Roy. Soc. Med. **29**:313 (Feb.)) 1936.

86. (*a*) Rosenthal, S. M.: Chemotherapy of Certain Infections with Sulfanilamide and Related Compounds, M. Ann. District of Columbia **6**:337 (Dec.) 1937. (*b*) Rosenthal, Bauer and Branham.[45]

87. Nitti, F.; Bovet, D., and Depierre, F.: Action des dérivés du p-aminophénylsulfamide (1162 F) sur les streptocoques hémolytiques in vitro, Compt. rend. Soc. de biol. **124**:16, 1937.

88. Buttle, G. A. H.; Parish, H. J.; McLeod, M., and Stephenson, D.: The Chemotherapy of Typhoid and Some Other Non-Streptococcal Infections in Mice, Lancet **1**:681 (March 20) 1937.

89. Footnote deleted.

90. Gross, P., and Cooper, F. B.: p-Aminobenzenesulfonamide and Antipneumococcal Serum Therapy in Type I Pneumococcal Infections of Rats, Proc. Soc. Exper. Biol. & Med. **36**:535 (May) 1937.

bronchially with type I (Neufeld) pneumococci. The mortality was reduced from 93 per cent in the control group to 21 per cent in the groups treated with serum or sulfanilamide and to 14 per cent in the group treated with both serum and the drug. Since the best therapeutic results were obtained by using a combination of serum and drug, Cooper and Gross [91] assumed that the two methods of treatment were synergistic. They found sulfanilamide was at least as effective as specific antiserum in the treatment of pneumonia caused by infection with type II pneumococci. The combination of sulfanilamide and serum was no more effective than sulfanilamide alone. Contrary to the observations in rabbits (Locke and Mellon), in rats vitamin C alone or in any combination tried was ineffective. Gross and Cooper [92] produced pneumonia in rats by intratracheal infection with type III pneumococci and found a mortality of 85.7 per cent in the untreated group while the mortality in the rats treated with sulfanilamide was 23.1 per cent. Buttle and his associates [88] emphasized that the protection against pneumococci with sulfanilamide was in no instance comparable to that obtained in hemolytic streptococcic and meningococcic infections.

Kreidler [93] concluded that if sulfanilamide is given orally to rabbits in adequate doses early in the course of experimental dermal infection with Pneumococcus type I the drug eliminates the micro-organisms from the blood stream, reduces the fever, cures the local lesion and favors recovery in most of the treated animals. Branham and Rosenthal [94] on the basis of experiments on mice, found that therapy which combined the use of serum and sulfanilamide, on the whole, yielded better results in pneumococcic infections than therapy with either alone. Schmidt [95] expressed the belief that the work of Rosenthal [86] and Cooper, Gross and Mellon [40] justifies the use of sulfanilamide in treating infections with other types of pneumococci—IV to XXXII—and particularly those types for which potent antiserums are not readily available. Schmidt's experiments demonstrated that sulfanilamide is

91. Cooper, F. B., and Gross, P.: Sulfanilamide, Antipneumococcus Serum and Vitamin C Therapy in Type II Pneumococcal Pneumonia of Rats, Proc. Soc. Exper. Biol. & Med. **36**:774 (June) 1937.

92. Gross, P., and Cooper, F. B.: Efficacy of *p*-Aminobenzenesulfonamide in Experimental Type III Pneumococcus Pneumonia in Rats, Proc. Soc. Exper. Biol. & Med. **36**:225 (April) 1937.

93. Kreidler, W. A.: Treatment of Pneumococcal Infections in Rabbits with Sulfanilamide, Proc. Soc. Exper. Biol. & Med. **37**:146 (Oct.) 1937.

94. Branham, S. E., and Rosenthal, S. M.: Studies in Chemotherapy: V. Sulfanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice, Pub. Health Rep. **52**:685 (May 28) 1937.

95. Schmidt, L. H.: Use of Sulfanilamide in the Treatment of Type XIV Pneumococcus Infections in Mice, Proc. Soc. Exper. Biol. & Med. **37**:205 (Oct.) 1937.

effective as a therapeutic agent for the treatment of mice infected with type XIV pneumococci. Whitby [76b] found in the treatment of mice infected with type I pneumococci that the effectiveness of sulfanilamide was surpassed by two diaminoanilide compounds. Rosenthal,[51] as mentioned previously, stated that the bacteriostatic and bactericidal action of sulfanilamide on pneumococci in vitro is adequate to explain its chemotherapeutic effect on animals.

Buttle [39a] first demonstrated the protective and curative properties of sulfanilamide against meningococcic infections in mice. Proom [74] concluded that sulfanilamide was equally effective against group I and group II meningococci but noted a much lower degree of protection if the administration of the drug was delayed for a few hours. The early oral administration of the drug prevented the development of septicemia and death in mice infected with meningococci. He advised the prophylactic use of sulfanilamide in meningococcic epidemics, since in man, the spread of infection from the nasopharynx to the meninges is most probably via the blood stream. Rosenthal, Bauer and Branham [45] found that disulfanilamide (sulfanilylsulfanilamide, paraaminobenzenesulfonylparaaaminobenzenesulfonamide) administered subcutaneously was more effective than sulfanilamide, but they were able to confirm Proom's findings. Neter [96] demonstrated a bacteriostatic effect of sulfanilamide on meningococci present in spinal fluid obtained from patients with meningococcic meningitis. Levaditi and Vaisman [97] found that sulfanilamide was curative in experimental infections induced by meningococci (types A, B, and C) in mucin. Whitby [76b] found sulfonanilide tartrate as effective as sulfanilamide in experimental meningococcic infections.

Buttle [88] reported the protection of mice against multiple lethal doses of Bacterium typhosum and Bacterium paratyphosum B with sulfanilamide. There was also some degree of protection against Bacterium aertrycke, Friedländer's bacillus, Pasteurella pseudotuberculosis and Pasteurella septica. In no instance, however, were the results of the treatment as satisfactory as in hemolytic streptococcic and meningococcic infections. Helmholz [66c] showed that with sulfanilamide in concentrations easily obtainable by oral administration the urine is rendered bactericidal for Esch. coli, Aerobacter aerogenes and organisms of the proteus and Pseudomonas groups. The drug was strikingly ineffective against infections with Str. faecalis. Albright, Dienes and Sulkowitch [98]

96. Neter, E.: Bacteriostatic Action of Sulfanilamide upon Meningococcus in Spinal Fluid, Proc. Soc. Exper. Biol. & Med. **38**:37 (Feb.) 1938.

97. Levaditi, C., and Vaisman, A.: Chimiothérapie de l'infection méningococcique expérimentale de la souris, Compt. rend. Soc. de biol. **125**:604, 1937.

98. Albright, F.; Dienes, L., and Sulkowitch, H. W.: Pyelonephritis with Nephrocalcinosis Caused by Haemophilus Influenzae and Alleviated by Sulfanilamide: Report of Two Cases, J. A. M. A. **110**:257 (Jan. 29) 1938.

found that sulfanilamide therapy promptly eliminated Haemophilus influenzae from the urine. Rosenthal [51] demonstrated the lack of effect of sulfanilamide upon the growth of Staphylococcus albus and Esch. coli. Nitti, Bovet and Depierre, [87] Levaditi [29b] and Long and Bliss [12f] have shown that the drug is ineffective against the Salmonella types. Bliss and Long,[99] however, protected mice against intraperitoneal injections of Clostridium welchii by previously administering sulfanilamide by the same route. Campbell [100] found no evidence that sulfanilamide has an effect on experimental syphilis in the rabbit. Rich and Follis [101] have described an inhibitory effect of the drug on the development of experimental tuberculosis in the guinea pig. Negative results were obtained on mice with Trypanosoma equiperdum and on canaries with avian malaria.[88]

It is of some interest that the effect of sulfanilamide on the metabolism of bacteria was studied by Barron and Jacobs.[102] Since the oxidized forms (the original prontosil and prontosil soluble) were found devoid of bactericidal properties, it has been assumed that these drugs become active by their reduction in the animal body.[41a] Barron and Jacobs found that the original prontosil had no effect on the metabolism of hemolytic streptococci, Bacillus coli, Friedländer's bacillus or gonococci. Sulfanilamide had a slight inhibitory effect on the oxidation of dextrose by hemolytic streptococci and on the oxidation of dextrose and lactate by Friedländer's bacillus.

CLINICAL OBSERVATIONS AND DOSAGE

Long and Bliss [46a] at first concluded from their experimental and clinical observations on the treatment of streptococcic infections that about forty-eight hours is required before maximum therapeutic effects can be obtained with sulfanilamide or its derivatives. Because of this time factor, they recommended that treatment be instituted immediately in infections due to hemolytic streptococci. They also observed that striking results could not be expected for patients with far advanced infections or for those already moribund. They [16] were convinced that with hemolytic streptococcic meningitis, peritonitis or septicemia or with meningococcic meningitis or septicemia the gravity of the prognosis

99. (*a*) Long, P. H., and Bliss, E. A.: Observations on Experimental and Clinical Use of Sulfanilamide in Treatment of Certain Infections, Canad. M. A. J. **37**:457 (Nov.) 1937. (*b*) Bliss and Long.[54]

100. Campbell, A. D.: A Note on the Failure of Sulfanilamide to Affect Syphilis in the Rabbit, Am. J. Syph., Gonor. & Ven. Dis. **21**:524 (Sept.) 1937.

101. Rich, A. R., and Follis, R. H., Jr.: The Inhibitory Effect of Sulfanilamide on the Development of Experimental Tuberculosis in the Guinea Pig, Bull. Johns Hopkins Hosp. **62**:77 (Jan.) 1938.

102. Barron, E. S. G., and Jacobs, H. R.: Effect of Prontosil and Prontylin on Metabolism of Bacteria, Proc. Soc. Exper. Biol. & Med. **37**:10 (Oct.) 1937.

warranted a disregard of all possible toxic effects of sulfanilamide in an attempt to control the infections as rapidly as possible. For patients weighing 100 pounds (45 Kg.) or more, an initial dose of from ten to sixteen 5 grain (0.32 Gm.) tablets was employed; the initial dose was intended to give a concentration of sulfanilamide in the blood of about 10 mg. per hundred cubic centimeters within four hours. To maintain this level, three 5 grain (0.32 Gm.) tablets were administered every four hours. Patients weighing from 50 to 90 pounds (23 to 41 Kg.) were given an initial dose of six to ten 5 grain (0.32 Gm.) tablets, followed by two or three 5 grain (0.32 Gm.) tablets every four hours. For children weighing from 25 to 50 pounds (11 to 23 Kg.) four to six 5 grain (0.32 Gm.) tablets were used an as initial dose and one or two 5 grain (0.32 Gm.) tablets employed every four hours as a maintenance dose. The maintenance dose may vary widely owing to the different rates of excretion in various persons.

In man, the absorption of sulfanilamide is apparently complete from the gastrointestinal tract in four hours. This is the basis for the selection of a four hour interval for maintenance doses. Subcutaneous administration of sulfanilamide is not followed by a higher concentration in the blood than is oral administration, so that parenteral administration is necessary only when the patient is nauseated or unconscious or fails to show a concentration of sulfanilamide in the blood of 8 to 10 mg. per hundred cubic centimeters because of faulty absorption. For parenteral use, the required amount of sterile physiologic solution of sodium chloride is brought to the boiling point, and when boiling ceases 0.8 to 1 Gm. of sulfanilamide is added for each hundred cubic centimeters of saline solution. The solution is agitated to facilitate solution of the sulfanilamide, cooled to 37 C. and administered by hypodermoclysis. Long and Bliss [16] recommended that for adults the initial hypodermoclysis should consist of 500 cc. of a 1 per cent solution, followed by 300 cc. at eight hour intervals during the first twenty-four hours. Persons weighing from 50 to 90 pounds (23 to 41 Kg.) received 200 to 400 cc. as an initial dose, followed by 200 cc. at eight hour intervals. An initial dose of 100 to 300 cc. was administered to children weighing from 25 to 50 pounds (11 to 23 Kg.) followed by 100 to 200 cc. of the solution at eight hour intervals. The authors recommended that babies receive a total of 1 Gm. of sulfanilamide per 10 pounds (4,540 Gm.) of body weight during the first twenty-four hours. In most instances, because of the rapid absorption of sulfanilamide from the intestinal tract it would seem that intravenous injection of the drug is unnecessary.

In infections of the meninges, intrathecal use of the drug has been advocated. Sulfanilamide is not irritating to the meninges and may

be administered according to the technic employed for giving antiserums by this route. Since the drug is present in the cerebrospinal fluid within a few hours of administration by mouth and in concentration only slightly lower than that in the blood, the necessity for intrathecal administration is infrequent. For intrathecal use, a concentration of 0.8 to 1.0 per cent in physiologic solution of sodium chloride is used. After preliminary spinal drainage, 15 to 25 cc. of this solution, at body temperature, is permitted to flow into the spinal canal by gravity. Positive pressure should never be employed, and the amount of sulfanilamide solution used should be 5 to 10 cc. less than the amount of cerebrospinal fluid withdrawn.

As has been the case with most new therapeutic agents, overdosage has led to unnecessary side effects. Long and Bliss [16] found that moderately severe streptococcic infections in adults may be controlled by administering three 5 grain (0.32 Gm.) tablets of sulfanilamide at four hour intervals, while mild streptococcic infections may be controlled with one or two 5 grain (0.32 Gm.) tablets at four hour intervals. The amount of sulfanilamide should be decreased as soon as definite clinical improvement is noted. Increased doses should follow the absence of clinical improvement or the recurrence of the infection.

Schwentker, Clason, Morgan, Lindsay and Long [81a] regarded prontosil soluble as unsuitable for intraspinal injection because it was definitely irritating to the meninges and frequently caused a marked cellular reaction with a distinct elevation of temperature. They recommended surgical procedures to eradicate septic foci in cases of streptococcic meningitis as an adjunct to specific therapy, but since the patients are poor surgical risks they felt that extensive surgical intervention should not be resorted to until the infection has been brought under control by the specific therapy. Ballenger, Elder and McDonald [103] have suggested the use of artificial fever to supplement the use of a chemical agent after their excellent results in cases of resistant gonococcic infection. Their patients chosen for thermochemotherapy were persons who failed to respond to artificial fever or whom sulfanilamide failed to benefit.

Basman and Perley [104] emphasized the fact that one cannot rely on oral administration alone in treating very sick infants. They recommended supportive treatment in addition to sulfanilamide, suggesting isotonic sodium lactate, to relieve severe acidosis, lactate-Ringer and dextrose solutions, to relieve or prevent dehydration, and blood transfu-

103. Ballenger, E. G.; Elder, O. F., and McDonald, H. P.: Sulfanilamide and Thermotherapy in Gonococcic Infections: Preliminary Report, J. A. M. A. **109**: 1037 (Sept. 25) 1937.

104. Basman, J., and Perley, A. M.: Report of Patients Treated with Sulfanilamide at the St. Louis Children's Hospital, J. Pediat. **11**:212 (Aug.) 1937.

sions. They investigated the solubility of crystalline sulfanilamide in Ringer's solution, lactate-Ringer solution, molar solution of racemic sodium lactate and 10 per cent dextrose solution. Solutions of 0.25, 0.5, 0.75 and 1 per cent sulfanilamide were made in each of these solutions, heated one-half hour in a boiling water bath and allowed to cool. All the solutions remained clear, and no change in hydrogen ion concentration was detectable in the isotonic solutions of sodium lactate or lactate-Ringer solution. Long and Bliss [105] have suggested that in cases of severe infection in which the immediate prognosis is grave both parenteral and oral administration of sulfanilamide may be used. For moderately severe infections either parenteral or oral administration may be employed. For mild or relatively chronic streptococcic infections, oral administration alone is adequate and frequently one-half to two-thirds the estimated dose is effective.

TOXIC MANIFESTATIONS

Reports of toxicity for experimental animals began to appear soon after the introduction of sulfanilamide and related compounds as chemotherapeutic agents. The reports of deleterious effects in man and an increasing array of side effects have become so numerous as to outnumber case reports and perhaps result in overemphasis. Domagk [11] reported that mice and dogs tolerate 0.5 Gm. of the original prontosil given orally, while cats tolerate only 0.2 Gm. per kilogram of body weight; the urine of dogs which were given varying amounts of the same drug over a period of fourteen days showed no red or white cells or casts. Buttle, Gray and Stephenson [39a] found the original prontosil innocuous for mice when oral doses of 0.6 Gm. per kilogram of body weight were used; larger doses, 1.25 and 5 Gm. per kilogram, proved fatal to the majority of mice. The experimenters gave sulfanilamide orally to mice and found that oral administration of 2.5 Gm. per kilogram was well tolerated but that 5 Gm. per kilogram killed 2 to 6 mice and 10 Gm. killed every mouse. The Tréfouëls, Nitti and Bovet [106] found sulfanilamide to possess negligible toxicity for animals, a finding corroborated by Bloch-Michel.[34] Proom,[74] using sulfanilamide in experimental work on animals, found it toxic when used intraperitoneally but administered it satisfactorily by mouth and subcutaneously. Whitby [76b] and Halpern and Mayer [107] observed toxic properties, and the latter noted an effect on the nervous system. In cases of acute poisoning, Hawking [52] found involvement of the central nervous system, but the other organs presented no demonstrable change; large doses

105. Long and Bliss (footnotes 46*a* and 99*a*).

106. Tréfouël, Tréfouël, Nitti and Bovet (footnotes 12*a* and 56*b*).

107. Halpern, B. N., and Mayer, R. L.: Toxicité expérimentale comparée de quelques substances antistreptococciques, Presse méd. **45**:747 (May 19) 1937.

in the peritoneal cavity had no irritating effect. Rosenthal [79a] reported 6 Gm. per kilogram of body weight given subcutaneously in olive oil to mice as the fatal dose. Two grams per kilogram produced spastic movements of the extremities, flexion of the spine, excitability and incoordination, which disappeared after twelve hours.

Raiziss, Severac and Moetsch [79] found that mice tolerated well subcutaneous doses of 1 to 2 Gm. per kilogram of body weight, while 2.5 to 3 Gm. proved a fatal dose. Hageman [108] gave mice large parenteral doses of sulfanilamide over a period of fourteen days, and at the end of that time 1 of the surviving animals was killed. Of the remaining mice, 1 was killed each week thereafter. The drug in large doses was not well tolerated, producing unsteadiness, incoordination, paralysis, acute anterior flexion of the spine, spastic extension of the legs, prostration, convulsions and sometimes death. When smaller doses were given, such symptoms were transient, coming on one-half to one hour after injection and disappearing in twelve to eighteen hours. Sulfanilamide suspended in saline solution when injected intraperitoneally into mice produced a fibroblastic foreign body reaction, with crystals scattered through the area of reaction; these areas appeared as milky white spots on the surfaces of the liver, spleen and peritoneum. The liver and kidneys, however, presented no pathologic change. Hemosiderin, in varying amounts, was found adjacent to the malpighian bodies, and the hemosiderin was roughly proportional to the size of the fatal dose and the duration of life after the onset of exposure. A greater incidence of eosinophils was noted in the bone marrow of the animals exposed to sulfanilamide. Barlow [109] found the 50 per cent oral minimum lethal dose for sulfanilamide given in suspension in acacia was 6.25 Gm. per kilogram of body weight for mice; the minimum lethal dose for sulfanilamide given by the subcutaneous route was found to be 2.75 to 4 Gm. per kilogram of body weight for mice.

Certain toxic manifestations with full doses of sulfanilamide or related compounds have been recognized since their first clinical use. Weakness, dizziness, tinnitus, lassitude, anorexia, general malaise, nausea, cyanosis, acidosis, sulfhemoglobinemia and fever were commonly encountered, but it was generally considered unnecessary to discontinue the drug when the milder symptoms appeared. Death following administration of sulfanilamide has been repeatedly reported in the literature. Frost [110] reported a case of sulfhemoglobinemia result-

108. Hageman, P. O.: Toxicity of Sulfanilamide: A Study of the Pathological Lesions in White Mice, Proc. Soc. Exper. Biol. & Med. **37**:119 (Oct.) 1937.

109. Barlow, O. W.: Relative Toxicities and Therapeutic Values of Three Chemotherapeutic Agents of Sulphonamide Type, Proc. Soc. Exper. Biol. & Med. **37**:315 (Nov.) 1937.

110. Frost, L. B. D.: Sulfhemoglobinemia Following Antistreptococcal Therapy, Lancet **1**:510 (Feb. 27) 1937.

ing in death. Borst [111] Young, [112] Model,[113] Schwartz, Garvin and Koletsky [114] and Berg and Holtzman [115] reported deaths due to agranulocytosis. O'Connell [116] reported a patient dying of edema of the glottis and agranulocytosis after receiving 365 grains (23.65 Gm.) of sulfanilamide in a period of seven days, but more of the drug may have been taken unofficially. Granulocytopenia following sulfanilamide therapy was reported by McIntosh, Wilcox and Wright [117] and Mitchell and Trachsler.[118] Leukopenia due to sulfanilamide has been reported by Mossel,[119] Plu ner,[120] Trumper [121] and Bigler, Clifton and Werner.[61] Bigler [122] found that sulfanilamide never increased the leukocyte count, while a depression of the white blood cells was common, there being a marked absolute reduction of all the cellular elements without any characteristic relative change in the proportion of the different white blood cells as studied by the Schilling count.

Harvey and Janeway [123] reported 3 cases in which acute hemolytic anemia developed during the administration of the drug; all 3 patients recovered promptly after blood transfusions. Anemia, with the appearance of nucleated red blood cells, polychromasia and moderate anisocy-

111. Borst, J. G. G.: Death from Agranulocytosis After Treatment with Prontosil Flavum, Lancet **1**:1519 (June 26) 1937.

112. Young, C. J.: Agranulocytosis and Para-Aminobenzenesulphonamide, Brit. M. J. **2**:105 (July 17) 1937.

113. Model, A.: Agranulocytosis and Para-Amino-Benzene-Sulfonamide, Brit. M. J. **2**:295 (Aug. 7) 1937.

114. Schwartz, W. F.; Garvin, C. F., and Koletsky, S.: Fatal Granulocytopenia from Sulfanilamide, J. A. M. A. **110**:368 (Jan. 29) 1938.

115. Berg, S., and Holtzman, M.: Fatal Granulocytopenia Following Sulfanilamide Therapy, J. A. M. A. **110**:370 (Jan. 29) 1938.

116. O'Connell, J. T.: Sulfanilamide Poisoning: Report of Fatal Case, U. S. Nav. M. Bull. **36**:61 (Jan.) 1938.

117. McIntosh, R.; Wilcox, D. A., and Wright, F. H.: Results of Sulfanilamide Treatment at the Babies Hospital, New York City, J. Pediat. **11**:167 (Aug.) 1937.

118. Mitchell, A. G., and Trachsler, W. H.: Report on the Use of Sulfanilamide and Its Derivatives at the Children's Hospital Cincinnati, J. Pediat. **11**:183 (Aug.) 1937.

119. Mossell, B. F.: Studies on the Use of Prontylin in Rheumatic Fever, New England J. Med. **216**:487 (March 18) 1937.

120. Plumer, H. E.: Prontylin and Prontosil, New England J. Med. **216**:711 (April 22) 1937.

121. Trumper, A.: Prontylin and Prontosil, New England J. Med. **216**:857 (May 13) 1937.

122. Bigler, J. A.: Blood Cell Response to Sulfanilamide Therapy, Ann. Otol., Rhin. & Laryng. **47**:219 (March) 1938.

123. Harvey, A. M., and Janeway, C. A.: The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide (Para-Aminobenzenesulfonamide), J. A. M. A. **109**:12 (July 2) 1937.

tosis, as the result of treatment with sulfanilamide was reported by Weinberg, Mellon and Shinn.[49] Kohn [124] reported the occurrence of acute hemolytic anemia during treatment with the drug. Cyanosis following administration of sulfanilamide was noted by Colebrook and Kenny,[12e] Harvey and Janeway [123] and Marshall and Walzl.[125] Tarbell [126] described cyanosis with fever in a patient with diarrhea following sulfanilamide therapy.

Colebrook and Kenny [12e] reported the occurrence of cyanosis and sulfhemoglobinemia in 3 patients treated with the original prontosil. All these patients had taken magnesium sulfate. Paton and Eaton [127] found that in most persons the administration of magnesium sulfate simultaneously with, or within two or three days preceding, the administration of sulfanilamide gives rise to sulfhemoglobinemia. They found the removal of sulfhemoglobin from the blood to be much slower than the removal of methemoglobin. The former could be detected six weeks after the administration of sulfanilamide ceased, while methemoglobin disappeared in about twenty-four hours. They felt that the detection of sulfhemoglobinemia is more accurately made by spectroscopic examination of the blood than by the clinical observation of cyanosis and recommended blood transfusion if the patient's life is endangered, since oxygen, although of some value in methemoglobinemia, is of no value in cases of severe sulfhemoglobinemia. Archer and Discombe [128] found that any treatment producing a liquid stool accelerates the formation of sulfhemoglobinemia. The combination of hemoglobin with the hydrogen sulfide absorbed from the intestinal tract results in intracorpuscular sulfhemoglobinemia; the reaction is catalyzed by the drug circulating in the blood. Purgation diminishes the normal absorption of protein products of digestion in the small intestine, resulting in increased putrefaction in the colon and a production of hydrogen sulfide in great excess. Archer and Discombe stated that the development of sulfhemoglobinemia can be prevented or delayed by cleansing the colon with enemas before treatment is started, by using a low residue diet of adequate caloric value, by eliminating eggs from the diet and by giving regular large doses of liquid petrolatum.

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124. Kohn, S. E.: Acute Hemolytic Anemia During Treatment with Sulfanilamide, J. A. M. A. **109**:105 (Sept. 25) 1937.

125. Marshall, E. K., Jr., and Walzl, E. M.: Cyanosis from Sulfanilamide, Bull. Johns Hopkins Hosp. **61**:140 (Aug.) 1937.

126. Tarbell, H. A.: Sulfanilamide Must Be Used with Care: Case Report, J. M. Soc. New Jersey **34**:506 (Aug.) 1937.

127. Paton, J. P. J., and Eaton, J. C.: Sulfhemoglobinemia and Methemoglobinemia Following Administration of *p*-Aminobenzenesulfonamide, Lancet **1**: 1159 (May 15) 1937.

128. Archer, H. E., and Discombe, G.: Sulfhemoglobinemia: Its Cause and Prevention, with Especial Reference to Treatment with Sulfanilamide, Lancet **2**: 432 (Aug. 21) 1937.

Colebrook and Kenny [77a] and Whitby [76b] noted the occurrence of sulfhemoglobinemia. Discombe [129] observed sulfhemoglobinemia in 6 of 7 patients receiving over 5 Gm. of the drug; association with magnesium sulfate was shown in all 6 cases, and in 1 the salt was merely used as a skin dressing. Colebrook and Purdie [130] in examining the blood of 53 patients with cyanosis following sulfanilamide therapy found sulfhemoglobinemia in 13, methemoglobinemia in 24 and both in 8. Methemoglobinemia following administration of sulfanilamide was considered and reported by Dees and Colston,[66g] Paton and Eaton,[127] Kenny [131] and Hageman.[132] Bensley and Ross [133] demonstrated that methemoglobinemia is not necessarily related to the amount of the dose of sulfanilamide, and that in some cases anoxemia may be aggravated by anemia or methemoglobinemia. Mull and Smith [134] described a patient who suffered not only a sharp drop in the oxygen content of the blood but also a distinct fall in the capacity of the blood for absorbing oxygen. The blood showed a peculiar color when aerated, never attaining the bright red of normal oxygenated blood. Marshall and Walzl [125] found that clinical cyanosis does not necessarily involve a decrease in oxygen-carrying capacity of the blood or the presence of nonfunctional iron pigment and stated that a black oxidation product of the drug stained the erythrocytes.

The occurrence of acidosis during sulfanilamide therapy has been discussed at length by Southworth,[135] Dees and Colston [66g] and Harvey and Janeway.[123] Borst [111] reported the occurrence of thrombopenic purpura following sulfanilamide therapy. Schonberg [136] observed purpuric and scarlatiniform eruption in 1 case in which one 5 grain

129. Discombe, G.: Sulfhemoglobinemia Following Sulfanilamide Treatment, Lancet **1**:626 (March 13) 1937.

130. Colebrook, L., and Purdie, A. W.: Treatment of One Hundred and Six Cases of Puerperal Fever by Sulphanilamide (Streptocide), Lancet **2**:1237 (Nov. 27); 1291 (Dec. 4) 1937.

131. Kenny, M.; Johnston, F. D.; von Haebler, T., and Miles, A. A.: *p*-Aminobenzenesulphonamide in Treatment of Bacterium Coli Infections of Urinary Tract, with Note on Two-Plate Bacterial Count, Lancet **2**:119 (July 17) 1937.

132. Hageman, P. O.: Clinical Experience in the Use of Sulfanilamide at the New Haven Hospital, J. Pediat. **11**:195 (Aug.) 1937.

133. Bensley, E. H., and Ross, J. B.: Methaemoglobinemia Due to Sulphanilamide, J. A. M. A. **109**:1035 (Sept. 25) 1937.

134. Mull, J. W., and Smith, J. T.: Effect of Sulfanilamide on the Oxygen Capacity of the Blood, J. A. M. A. **110**:439 (Feb. 5) 1938.

135. Southworth, H.: Acidosis Associated with the Administration of Para-Aminobenzene-Sulphonamide (Prontylin), Proc. Soc. Exper. Biol. & Med. **36**: 58 (Feb.) 1937.

136. Schonberg, I. L.: Purpuric and Scarlatiniform Eruption Following Sulfanilamide, J. A. M. A. **109**:1035 (Sept. 25) 1937.

(0.32 Gm.) tablet precipitated marked allergic symptoms. Hageman and Blake [137] reported a case in which thrombopenic purpura developed after the patient had taken sulfanilamide, phenyl salicylate and acetophenetidin in small doses while being treated for pharyngitis and cervical adenitis. Newman and Sharlit [138] reported the photosensitizing action of sulfanilamide on the skin. They found that withdrawal of both the drug and sunlight resulted in complete disappearance of the eruption before the sensitizing influence of the irradiation had been dissipated. Brunsting,[139] Menville and Archinard,[140] Frank,[141] Grosjean [142] and Colebrook and Purdie [130] have commented on the occurrence of this photosensitizing action of the drug.

Menville and Archinard [140] described 4 cases with maculopapular eruption, associated with severe itching and the formation of minute unerupted vesicles. In 1 case the rash was associated with severe chills, fever and leukocytosis. The rash disappeared within several days when the drug was discontinued. Goodman and Levy [143] reported 2 cases of toxicodermatosis, in 1 of which hemorrhagic lesions developed, an indication that sulfanilamide may have a vasculotoxic property. Schwentker and Gelman [144] observed the development of a rash in 10 of 180 patients. In some cases, the rash was recognized as early as the third day of medication. In one half of the cases, the rash appeared between the tenth and the fourteenth day. The eruption was morbilliform and made up of maculopapular lesions, brownish and slightly raised. Almost the entire surface of the body was covered, but at times the lesions were limited to the buttocks and legs. Occasionally, the eruption was seen on the palms of the hand and soles of the feet, while the mucous membranes were unaffected. The eruption faded rapidly after the drug was discontinued.

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137. Hageman, P. O., and Blake, F. G.: Clinical Experience with Sulfanilamide in the Treatment of Beta Hemolytic Streptococcic Infections, Am. J. M. Sc. **195**:163 (Feb.) 1938.

138. Newman, B. A., and Sharlit, H.: Sulfanilamide: Photosensitizing Agent of the Skin, J. A. M. A. **109**:1036 (Sept. 25) 1937.

139. Brunsting, L. A.: Sulfanilamide Dermatitis: Question of Relation to Photosensitivity, Proc. Staff Meet., Mayo Clin. **12**:614 (Sept. 29) 1937.

140. Menville, J. G., and Archinard, J. J.: Skin Eruptions in Patients Receiving Sulfanilamide: Report of Four Cases, J. A. M. A. **109**:1008 (Sept. 25) 1937.

141. Frank, L. J.: Dermatitis from Sulfanilamide, J. A. M. A. **109**:1011 (Sept. 25) 1937.

142. Grosjean, W. A.: The Sun and Sulfanilamide, J. A. M. A. **109**:1382 (Oct. 23) 1937.

143. Goodman, M. H., and Levy, C. S.: The Development of Cutaneous Eruption (Toxicodermatosis) During the Administration of Sulfanilamide: Report of Two Cases, J. A. M. A. **109**:1009 (Sept. 25) 1937.

144. Schwentker, F. F., and Gelman, S.: Sulfanilamide Rash, Bull. Johns Hopkins Hosp. **61**:136 (Aug.) 1937.

Schwentker, Gelman and Long [145] occasionally noted a morbilliform rash in patients given the drug for streptococcic infections. Such a rash was noted by Hageman [132] and appeared in one half of his cases in which a febrile complication followed the use of the drug. Severe dermatitis medicamentosa was reported by Finney,[146] and Myers [147] reported exfoliative dermatitis following administration of sulfanilamide. Morbilliform eruptions and hyperpyrexia during the course of sulfanilamide therapy have been reported by Unshelm,[65a] Hageman and Blake [148] and Mainzer.[149] It is generally agreed that the drug should be withdrawn with the development of jaundice or fever not attributable to the infection. Myers [147] obtained a positive patch test in his case of exfoliative dermatitis. Mitchell and Trachsler [118] observed maculopapular and morbilliform rashes. Hypersensitivity to sulfanilamide with urticarial lesions was described by Salvin.[150]

Fever due to administration of sulfanilamide was noted by Menville and Archinard,[140] Recknagel,[19] Tarbell,[126] Harvey and Janeway,[123] Grütz,[151] Felke, [152] Hageman [132] and Colebrook and his co-workers.[153] Hageman and Blake [148] observed a febrile reaction to sulfanilamide in 21 of 134 cases. The appearance of fever complicates differential diagnosis, and Hageman and Blake considered the similarity of the febrile response and associated reactions to those of serum sickness. Colebrook and Kenny [12e] and Whitby [76b] observed some irritation of the kidney by sulfanilamide. Hageman and Blake [137] found retention of nitrogen in 3 cases. In 2 the condition promptly subsided when the drug was withdrawn. In the third acute nephritis was present when the treatment was started; uremia later developed, and the patient died. A case of hematuria following large doses of prontosil and sulfanilamide was reported by Mitchell and Trachsler.[118]

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145. Schwentker, F. F.; Gelman, S., and Long, P. H.: The Treatment of Meningococcic Meningitis with Sulfanilamide: Preliminary Report, J. A. M. A. **108**:1407 (April 24) 1937.

146. Finney, J. O.: Severe Dermatitis Medicamentosa Following the Administration of Sulfanilamide, J. A. M. A. **109**:1982 (Dec. 11) 1937.

147. Myers, G. B.; Vonder Heide, E. C., and Balcerski, M.: Exfoliative Dermatitis Following Sulfanilamide, J. A. M. A. **109**:1983 (Dec. 11) 1937.

148. Hageman, P. O., and Blake, F. G.: Specific Febrile Reaction to Sulfanilamide: Drug Fever, J. A. M. A. **109**:642 (Aug. 28) 1937.

149. Mainzer, F. S.: Sulfanilamide Rash, Pennsylvania M. J. **41**:386 (Feb.) 1938.

150. Salvin, M.: Hypersensitivity to Sulfanilamide, J. A. M. A. **109**:1038 (Sept. 25) 1937.

151. Grütz, O.: Neue Grundlegung für die Gonorrhoebehandlung, München. med. Wchnschr. **84**:1201 (July 30) 1937.

152. Felke, H.: Die Chemotherapie der Gonorrhoe, Deutsche med. Wchnschr. **63**:1393 (Sept. 10) 1937.

153. Colebrook and Kenny.[77] Colebrook and Purdie.[130]

The occurrence of nausea, anorexia and diarrhea indicates a certain amount of reaction to the drug on the part of the gastrointestinal tract. Diarrhea was noted by Tarbell,[126] Recknagel [19] and Bucy.[154] Schneider [155] observed an unusually violent reaction, not only in the smooth muscle of the rectum, but also in the uterus and the bladder. Colebrook and Kenny [12e] and Long and Bliss [12f] noted an effect on the lower intestinal tract resulting in the urge to defecate. Harvey and Janeway [123] reported a depression of hepatic function, as determined by bromsulphalein tests. Hageman and Blake [137] described the occurrence of toxic hepatitis in 1 patient with probable chronic cholecystitis; recovery followed withdrawal of the drug.

Effects on the nervous system are relatively uncommon, but mental confusion was noted by Paton and Eaton [127] and the occurrence of toxic neuritis was reported by Bucy.[154] Hogan [156] observed psychosis precipitated by sulfanilamide in a case of gonococcic infection of the prostate in which treatment was continued over a period of three weeks. Nine hundred and forty grains (61 Gm.) was given during the first course and 280 grains (18 Gm.) during the second course, but the patient at no time received over 80 grains (5 Gm.) per day. The psychotic picture was first characterized by mild paranoid feelings, with apprehension and restlessness; later the psychosis became acute, with auditory and visual hallucinations. Improvement followed withdrawal of the drug. Clinical experience has shown that in most instances the milder toxic manifestations rapidly recede with reduction of the dose or withdrawal of the drug.

SULFANILAMIDE THERAPY FOR OTOLARYNGOLOGIC AND OTHER INFECTIONS

Because otolaryngologists are so frequently faced with the complicating factors of meningitis and septicemia, both preoperatively and postoperatively, the announcement of a new drug with undoubted value in the treatment of these dangerous infectious conditions commanded immediate attention. It was only by clinical trial, however, that the actual value of the drug could be estimated. Because of the excellent therapeutic effect of the drug on infections with beta hemolytic streptococci in animals, it was natural that its application to similar infections in man should be widely attempted. The evaluation of the curative effects of sulfanilamide is difficult on the basis of many case reports,

154. Bucy, P. C.: Toxic Optic Neuritis Resulting from Sulfanilamide, J. A. M. A. **109**:1007 (Sept. 25) 1937.

155. Schneider, E.: Unerwartete Wirkung von Prontosil auf glattmuskuläre Organe, Zentralbl. f. Gynäk. **60**:1832 (Aug. 1) 1936.

156. Hogan, B. W.: Psychosis Precipitated by Sulfanilamide, U. S. Nav. M Bull. **36**:60 (Jan.) 1938.

since other forms of treatment are so frequently administered at the same time as the drug and in many instances the latter is used only because of the severity or hopelessness of the infection.

Pharyngitis and Tonsillitis.—It is of interest to note that Brennemann [157] found in practically every case of a carrier of hemolytic streptococci sterile cultures for hemolytic streptococci, usually within twenty-four hours after the administration of sulfanilamide. In every case, however, the cultures again became positive one to six days after the drug was stopped.

The opinion of the majority of authors seems to attribute a favorable effect to the drug in both pharyngitis and tonsillitis when the infection is primarily due to hemolytic streptococci. The temperature usually regained a normal level within a few hours to three days after administration of the drug, but beta hemolytic streptococci, when present, persisted in the cultures of material from the throat in some instances for as long as four or five weeks. Watson-Williams,[158] however, while conceding the beneficial effect of sulfanilamide in 11 cases of streptococcic tonsillitis, found the results no better than those obtained with sodium salicylate. His results in the treatment of pharyngitis were good. Long and Bliss [46a] reported cures in 14 cases of tonsillitis and 5 cases of peritonsillar infection. Waring and Rettberg [159] found the drug beneficial in the treatment of streptococcic sore throat. Smith [160] stated that sulfanilamide had no prophylactic value in checking the spread of tonsillitis under epidemic conditions but was valuable in the treatment of streptococcic tonsillitis; he again noted that although infections with hemolytic streptococci were amenable to treatment with sulfanilamide, infections with Str. viridans were little if at all, affected.

Kenny and his co-workers [131] reported the development of tonsillitis in 2 patients who were being treated with the drug for bacteriuria. The immediate results of sulfanilamide therapy were good in 7 cases of tonsillitis reported by Hageman,[132] but hemolytic streptococci persisted in the cultures of material from the throat for as long as five weeks. Gallagher [161] treated 33 patients with epidemic streptococcic pharyngitis

157. Brennemann, J.: Report on Sulfanilamide from the Children's Memorial Hospital of Chicago, J. Pediat. **11**:238 (Aug.) 1937.

158. Watson-Williams, E.: Sulfanilamide in Treatment, Bristol Med.-Chir. J. **54**:209, 1937.

159. Waring, J. J., and Rettberg, W. A.: Sulfanilamide in Treatment of Streptococcic Infections: Good Effects and Bad Effects, Rocky Mountain M. J. **35**:26 (Jan.) 1938.

160. Smith, A.: Chemotherapy of Streptococcic Infections, Lancet **2**:1064 (Nov. 6) 1937.

161. Gallagher, J. R.: Observations on the Therapeutic Value of Sulfanilamide in Beta-Hemolytic-Streptococcic Pharyngitis, Am. J. M. Sc. **194**:830 (Dec.) 1937.

caused by strains of beta hemolytic streptococci of low virulence for mice. He found that the administration of doses of the drug equivalent to 1 Gm. of sulfanilamide per 10 Kg. of body weight early in the course of the disease apparently shortened the length of time during which cultures of material from the throat continued to reveal the bacteria. Basman and Perley [104] reported marked clinical improvement with some decrease in temperature when sulfanilamide was given in adequate doses. Pollock [162] stated that in 2 cases of hemolytic streptococcic sore throat the temperature dropped to normal within twelve hours and recovery was rapid and uneventful. McIntosh [117] found no striking effect on the clinical course of peritonsillar abscess when sulfanilamide was used. The drug may be of value when administered early in the course of the infection, but in the hands of most clinicians it has consistently failed to be effective after suppuration occurs.

Vincent's Infection.—Sinclair [163] found sulfanilamide of no value in Vincent's infection when used topically. No effect on Vincent's infection has been observed when the drug is administered by mouth.

Ludwig's Angina.—A 3 year old child with Ludwig's angina was treated with sulfanilamide by Fulghum.[164] The progress of the disease was arrested, and gradual regression of the swelling, without formation of pus, followed, with rapid return to a normal condition. On the other hand, Long and Bliss [46a] had 2 patients with Ludwig's angina who died within twenty and thirty-five hours respectively after the beginning of treatment with the drug.

Other Oral Infections.—Sinclair [163] reported that the powdered form of sulfanilamide was "successfully" applied in "dry socket," infected compound fracture of the mandible and osteomyelitis of the mandible. Livingston [165] was impressed with the effects of the drug in acute and subacute peridontal and periapical infections involving extractions, reporting 5 cases but offering no convincing evidence that there was any benefit. Paul [166] used prontosil album (sulfanilamide) to advantage in a case of osteomyelitis of the mandible. Gauss [167] reported the relief

162. Papers presented at the meeting of the Chicago Laryngological and Otological Society, Oct. 4, 1937, Ann. Otol., Rhin. & Laryng. **46**:1124 (Dec.) 1937.

163. Sinclair, J. A.: Preliminary Report on the Local Use of Sulfanilamide in the Treatment of Oral Lesions, J. Canad. Dent. A. **3**:571 (Nov.) 1937.

164. Fulghum, J. E.: Sulfanilamide Treatment of Ludwig's Angina, U. S. Nav. M. Bull. **36**:58 (Jan.) 1938.

165. Livingston, A.: Prontosil Album, Brit. Dent. J. **62**:638 (June 15) 1937.

166. Paul, A.: Sur un cas d'ostéomyelite mandibulaire au cours de la grossesse, Rev. de stomatol. **39**:819 (Nov.) 1937.

167. Gauss, E.: Ueber die Verwendung von Prontosil in der Zahnheilkunde, Zahnärztl. Rundschau **46**:1813 (Oct. 17) 1937.

of pain and retrogression of inflammatory symptoms in cases involving peridontitis, subperiosteal abscess, difficult eruptions or infected wounds. The course of stomatitis was arrested and favorable results were obtained in the treatment of stomatitis aphthosa. Feise [168] in a report based on experience with 50 cases, including subperiosteal and submucous abscesses of the maxillas and mandible, abscesses of the floor of the mouth, phlegmons, parotitis and various forms of stomatitis and paradontosis, concluded that the course and duration of the disease was favorably influenced in each instance and that operative intervention was frequently rendered unnecessary.

Adenitis.—Sulfanilamide appears to have little effect on suppurative adenitis, while favorable results may be encountered in the treatment of nonsuppurative adenitis. McIntosh [117] in a case of nonsuppurative adenitis observed the temperature fall to normal within forty-eight hours and the swelling of the glands subside rapidly, being impalpable in one week; in a second case, however, he obtained questionable results with the drug. In 2 cases of suppurative adenitis questionable results were presented. Hageman [132] found that in 1 of 7 cases of cervical adenitis in which treatment with sulfanilamide was employed incision and drainage were required. Relapse occurred in 1 instance, but response to a second course of the drug was satisfactory. In the remaining cases the condition subsided promptly. A review of the case reports makes it evident that adenitis due to the beta hemolytic streptococcus may or may not be amenable to treatment with sulfanilamide but that when surgical drainage is required the temperature remains elevated until drainage is accomplished.

Otitis Media.—In regard to otitis media the situation is too complex for satisfactory evaluation of the drug. Paracentesis was performed early in some instances, late in others. In general, results were better when the hemolytic streptococcus was present in pure culture than when mixed infections occurred. There is as yet no evidence that the drug prevents extension of the infection from the middle ear to the mastoid cells, although pediatricians in general feel that fewer mastoid infections followed infections of the middle ear when treatment with sulfanilamide was employed during the winter of 1937-1938. Watson-Williams [158] expressed the opinion that sulfanilamide is of definite value in the control of infections of the middle ear. Carey [169] treated 8 patients suffering from acute otitis media with adequate doses of the drug. Two

168. Feise, U.: Ueber die Anwendung von Prontosil in der zahnärztlichen Chirurgie, Deutsche zahnärztl. Wchnschr. **40**:307 (April 2) 1937.

169. Carey, B. W., Jr.: The Use of Para-Aminobenzenesulfonamide and Its Derivatives in Treatment of Infections Due to the B-Streptococcus Hemolyticus, the Meningococcus and the Gonococcus, J. Pediat. **11**:202 (Aug.) 1937.

of the 8 required mastoidectomy. Hageman and Blake [137] found that otitis media in 11 patients subsided promptly with sulfanilamide therapy and that mastoiditis did not develop in any instance after treatment was started. Long and Bliss [16] found that hemolytic streptococcic otitis media was very responsive to treatment with sulfanilamide. Livingston [162] found inadequate doses or too early cessation of administration of the drug responsible for some failures in the treatment of otitis media but observed 7 cases of acute suppurative otitis media in which no benefit was obtained by adequate doses. Basman and Perley [104] treated 9 patients with otitis media without mastoiditis, and in no instance did the infection go on to mastoiditis. Long and Bliss [47a] used sulfanilamide alone in the treatment of pneumococcic otitis media and mastoiditis. They observed that the drug has one-half the chemotherapeutic effect on pneumococcic infections that it has on hemolytic streptococcic infections of the middle ear and mastoid.

Mastoiditis.—The large number of cases of mastoiditis in the literature in which a favorable result with sulfanilamide therapy is reported may be somewhat misleading. It must be remembered that in many cases mastoiditis subsided without operation before sulfanilamide was available. In 64 cases in which a favorable reaction to the drug was reported 53 patients came to operation because it was indicated. Sulfanilamide seems to be of value, however, in those instances in which meningeal irritation is in evidence. Six patients with 2,000 to 4,000 cells in the cerebrospinal fluid and with destructive mastoiditis recovered without operation. The drug appears to be effective also in treating the cellulitis about mastoid wounds and above all in dealing with the complicating factors of meningitis and septicemia, especially when they are due to the beta hemolytic streptococci. In most instances exenteration of mastoid cells and, in the presence of infection of the blood stream, ligation of the internal jugular vein cannot be superseded by the administration of the drug alone.

Bernstein [170] obtained good clinical results with sulfanilamide in 5 cases of otitis media with mastoiditis. All 5 patients were operated on. Postoperative cellulitis and erysipeloid lesions responded well to the drug. In 1 case favorable results were obtained although a nonhemolytic streptococcus was cultured from the mastoid wound and cellulitis developed postoperatively. Long and Bliss [16] found that patients with acute hemolytic streptococcic mastoiditis were especially benefited during the postoperative course by adequate doses of sulfanilamide. In 1 of their cases, death occurred in spite of mastoidectomy, secondary mastoidectomy, exploration of the petrous portion of the temporal bone

170. Bernstein, S. S.: Report on the Use of Sulfanilamide at the Children's Hospital of Michigan, J. Pediat. **11**:198 (Aug.) 1937.

and adequate doses of sulfanilamide. The streptococci isolated from the patient were susceptible in vitro to the bacteriostatic effects of the drug. In a case of an adult the danger of discontinuing therapy too soon was demonstrated; meningeal invasion took place on the fourth day after treatment was stopped, but recovery followed resumption of the drug. In this case the drop in the carbon dioxide–combining power to 15.5 volumes per cent after 111 hours of treatment illustrated the effects of omitting base with sulfanilamide therapy. The normal carbon dioxide–combining power was soon reestablished with intensive alkali therapy. A third patient recovered promptly from hemolytic streptococcic meningitis secondary to otitis media when the drug was used.

Basman and Perley [104] noted that the outstanding feature of sulfanilamide therapy in the treatment of mastoiditis was the smooth postoperative course with lack of complications. They used sulfanilamide therapy in 15 cases of otitis media with mastoiditis. In 13 operation was performed, and in 2 the condition subsided without requiring operation. Hageman and Blake,[137] using the drug in 15 cases of mastoiditis, found mastoidectomy necessary in 2, and all the patients recovered. Neal and Appelbaum [171] reported 4 deaths in a series of 17 patients with otitis media and mastoiditis treated with sulfanilamide. Carey [169] reported no deaths in 4 patients with mastoiditis complicated by meningitis. Beta hemolytic streptococci were cultured from the mastoid wound in every case and from the cerebrospinal fluid in 2. The cerebrospinal fluid became sterile after twenty-four hours of treatment in each case, and in every instance the temperature became normal after the fifth day of sulfanilamide therapy. A patient with perisinal abscess complicating mastoiditis made an uneventful recovery when the perisinal abscess was drained at the time of the mastoidectomy and prontosil soluble and sulfanilamide were used immediately after operation. Brennemann [157] treated a mastoid abscess due to Staph. aureus with sulfanilamide for eight days, at which time the mastoid abscess had ceased to drain but the ear continued to drain.

Shambaugh [162] described a case in which paralysis of the sixth nerve developed one week after mastoidectomy. A profuse discharge from the middle ear continued for four months, although the mastoid incision healed within a few weeks of the operation. The paralysis of the sixth nerve disappeared, but roentgenograms showed a large area of cellular destruction in the petrous apex. Twenty-four hours after administration of sulfanilamide was begun, the discharge ceased, and the hearing became normal two weeks later. Jordan [162] reported the recovery of 3 patients for whom mastoidectomy was indicated when prontosil soluble was administered. Livingston [162] reported 5 cases of mastoiditis in which by the usual standards mastoidectomy would have been performed. All

171. Neal, J. B., and Appelbaum, E.: Experience with Sulfanilamide in Meningitis, Am. J. M. Sc. **195**:175 (Feb.) 1938.

the patients recovered promptly with sulfanilamide therapy. In pointing out that sulfanilamide may reduce the necessity of operative procedures, Livingston noted that in one hospital service 76 mastoidectomies were performed in 1935 and 59 in 1936, while in 1937 only 22 were done. In emphasizing the fact that not all the patients treated with sulfanilamide were benefited, he stated that the cases in which treatment was unsuccessful divided themselves into two groups. In the first, inadequate doses were given. The second comprised 7 cases of acute suppurative otitis media in which proper administration of sulfanilamide seemed to exert no beneficial effect.

Otogenic Meningitis.—The most convincing evidence of the effectiveness of sulfanilamide therapy in man has accrued from the clinical observations in cases of beta hemolytic streptococcic meningitis. Gray,[172] in 1935, reviewed the literature on streptococcic meningitis for the period from 1901 to 1935 and found 66 cases in which recovery was recorded. Tripoli [173] reported a mortality of 91.6 per cent, while Gray estimated the mortality at 97 per cent. Trachsler and his co-workers,[174] reviewing the literature to June 1937, found 39 instances of recovery in addition to the 66 reviewed by Gray and added 5 of their own, making a total of 110 recoveries. The number of recoveries from streptococcic meningitis since sulfanilamide has been available now exceeds the total number from 1901 to 1937.

The drug should obviously effect excellent clinical results in cases of meningitis due to the beta hemolytic streptococcus, but its value against other types of meningitis could not be accurately predicted. Many authors [175] had shown that sulfanilamide was an effective agent for treating human infections due to the beta hemolytic streptococcus. Mellon, Gross and Cooper [176] showed that the marked therapeutic effect of both prontosil soluble and sulfanilamide against hemolytic streptococci obtained for strains of both medium and high virulence. They

172. Gray, H. J.: Streptococcus Meningitis: Report of a Case with Recovery, J. A. M. A. **105**:92 (July 13) 1935.

173. Tripoli, C. J.: Bacterial Meningitis: Comparative Study of Various Therapeutic Measures, J. A. M. A. **106**:171 (Jan. 18) 1936.

174. Trachsler, W. H.; Frauenberger, G. S.; Wagner, C., and Mitchell, A. G.: Streptococcic Meningitis with Special Emphasis on Sulfanilamide Therapy, J. Pediat. **11**:248 (Aug.) 1937.

175. Patterson, D. C.: Experience with Prontosil and Prontylin, J. Connecticut M. Soc. **1**:358 (Aug.) 1937. Gardner, W. W.: Case Report: Streptococcus Hemolyticus Infection Treated with Sulfanilamide, New York State J. Med. **37**:1673 (Oct. 1) 1937. Willson, P.: Beta-Hemolytic Streptococcus Infection Treated with Para-Aminobenzenesulfonamide: Case, M. Ann. District of Columbia **6**:153 (June) 1937. Long and Bliss.[46] Colebrook and Kenny.[77a] Raiziss, Severac and Moetsch.[79] Footnote 81f. Peters and Havard.[81g] Waring and Rettberg.[159]

176. Mellon, R. R.; Gross, P., and Cooper, F. B.: Sulfanilamide and Prontosil in Hemolytic Streptococcus Infection, J. A. M. A. **108**:1858 (May 29) 1937.

also found that the drug resulted in localization and rapid healing of experimental intradermal hemolytic streptococcic infections, which in the untreated animal may disseminate with fatal results. Caussé, Loiseau and Gisselbrecht [177] reported in February 1936 the first recovery resulting from the use of the new drug. Arnold [178] reported a case of hemolytic streptococcic meningitis with mastoiditis and peripheral facial paralysis prior to operation. After sulfanilamide therapy, cultures of the spinal fluid became sterile in four days and had become sterile twenty-four hours before mastoidectomy was performed. The marked reduction in the cell count of the spinal fluid corroborated Schwentker's findings that the drug itself produces no cellular response in the leptomeninges. In this case the inflammatory reaction of the leptomeninges was greatly decreased after one intraspinal injection. Arnold suggested that intraspinal injection be continued until three negative cultures were obtained and that oral administration be continued ten days after the last positive culture of the spinal fluid. He was uncertain (February 1937) whether or not parenteral and oral administration of the drug would control infection in the central nervous system without intraspinal injection.

Lucas,[179] Vitenson and Konstam,[180] Schwentker and others,[81a] Draeseke and Raynor,[181] Martin and Delaunay,[182] Frazer,[183] Millet [184] and Long and Bliss [16] have reported the successful treatment of hemolytic streptococcic meningitis. Watson-Williams [158] treated 3 patients with such meningitis, of whom 2 died. Thompson [185] and Folsom [186]

177. Caussé, Loiseau and Gisselbrecht: Méningite purulente otogène à streptocoques hémolytiques, traitée exclusivement par un colorant azoïque, Guérison, Ann. d'oto-laryng., February 1936, p. 194.

178. Arnold, J. G., Jr.: Treatment of Hemolytic Streptococcus Meningitis with Para-Amino-Benzene-Sulfonamide, Ann. Int. Med. **10**:1198 (Feb.) 1937.

179. Lucas, C. F.: Haemolytic Streptococcal Meningitis Treated with Prontosil: Recovery, Brit. M. J. **1**:557 (March 13) 1937.

180. Vitenson, I., and Konstam, G.: Case of Streptococcal Meningitis Treated with Prontosil, Lancet **1**:870 (April 10) 1937.

181. Draeseke, G. C., and Raynor, E. F.: Case of Streptococcal Meningitis Treated with Prontosil, Canad. M. A. J. **36**:618 (June) 1937.

182. Martin, R., and Delaunay, A.: Action of Para-Amino-Phenyl-Sulfamide (Sulfanilamide) in Purulent Meningitis with Streptococci and Accessorily with Meningococci, Presse méd. **45**:1406 (Oct. 6) 1937.

183. Frazer, M. J. L.: Recovery from Streptococcal Meningitis After Prontosil, Brit. M. J. **1**:1023 (May 15) 1937.

184. Millet, J.: Hemolytic Streptococcus Meningitis: Report of Case with Recovery After Use of Sulfanilamide and Its Derivatives, New England J. Med. **217**:556 (Sept. 30) 1937.

185. Thompson, C. G.: Report of Case of Hemolytic Streptococcic Meningitis, with Recovery After Prolonged Use of Prontosil and Prontylin (Sulfanilamide), J. Connecticut M. Soc. **1**:363 (Aug.) 1937.

186. Folsom, T. G.: Streptococcic Meningitis: Review of a Case Treated Successfully with Sulfanilamide, West Virginia M. J. **34**:33 (Jan.) 1938.

have each reported a case with recovery. Anderson [187] reported recovery in a case of hemolytic streptococcic meningitis with otitis media and positive cultures of the spinal fluid. Weinberg, Mellon and Shinn [49] reported 2 cases with recovery, and Hageman and Blake [137] reported 5 cases, with recovery in 2. Friedman and Lieberman [188] reported postoperative streptococcic meningitis in a case of mastoid involvement with recovery. Mitchell and Trachsler [118] noted that 4 of 7 patients with streptococcic meningitis recovered, but Trachsler and others [174] observed that a patient not treated with sulfanilamide also recovered. Vaisberg [189] reported the recovery of a patient with acute mastoiditis complicated by hemolytic streptococcic meningitis. Godwin [190] reported 2 cases of hemolytic streptococcic meningitis with recovery, and 5 similar cases with recovery were reported by Carey.[169] Hodgins [191] reported a case of streptococcic septicemia with recovery. Kopetzky [192] recently reported that he had obtained better results in the treatment of otogenic meningitis with sulfanilamide than with any other drug, serum or vaccine. Combined with small transfusions, he stated, the drug is the best therapeutic agent he has employed. Bernheimer and Cooley [193] successfully treated a patient with streptococcic meningitis with sulfanilamide after exposing the dura of the middle fossa during the mastoidectomy and because of infiltrating thrombophlebitis ligating the internal jugular vein. Smith and others [194] reported the recovery after treatment with sulfanilamide of a patient with meningitis of otitic origin caused by an obligate anaerobic beta hemolytic streptococcus. Oral sulfanilamide therapy was relied on exclusively except for the first two days of the disease, when prontosil soluble was given intramuscularly.

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187. Anderson, E. D.: Hemolytic Streptococcus Meningitis: Report of a Case with Recovery After the Use of Prontosil and Sulfanilamide, J. A. M. A. **108:** 1591 (May 8) 1937.

188. Friedman, M. D., and Lieberman, L.: Severe Hemolytic Streptococcic Meningitis with Recovery After Use of Prontosil and Sulfanilamide, Ohio State M. J. **33:**1322 (Dec.) 1937.

189. Vaisberg, M.: The Use of Sulfanilamide in Acute Mastoiditis: Report of a Case, Laryngoscope **48:**54 (Jan.) 1938.

190. Godwin, D. E.: Two Cases of Streptococcus Hemolyticus Meningitis with Recovery Following the Use of Sulfanilamide, Laryngoscope **48:**59 (Jan.) 1938.

191. Hodgins, W. S.: Case of Streptococcus Septicemia, Canad. M. A. J. **37:** 174 (Aug.) 1937.

192. Kopetzky, S. J.: The Management and Treatment of Otogenic Meningitis, Ann. Otol., Rhin. & Laryng. **47:**117 (March) 1938.

193. Bernheimer, L. B., and Cooley, W.: Streptococcic Meningitis with Recovery, Arch. Otolaryng. **26:**687 (Dec.) 1937.

194. Smith, F. W., and others: Anaerobic Beta Hemolytic Streptococcus Meningitis of Otitic Origin Treated with Sulfanilamide and Culminating in Complete Recovery, J. A. M. A. **110:**887 (March 19) 1938.

Kopetzky [192] reported 3 cases of otogenic meningitis due to the hemolytic streptococcus. One patient was subjected to a radical apicectomy before sulfanilamide was given. This patient and 2 with otitic hydrocephalus recovered after adequate surgical measures were followed with sulfanilamide therapy. Galloway [162] reported 5 cases of hemolytic streptococcic meningitis in which recovery followed sulfanilamide therapy; in 2 of these, in which there were definite indications for mastoidectomy, the condition cleared up in a few days. Guttman [162] treated a patient with hemolytic streptococcic meningitis with sulfanilamide, and recovery followed. Woodman [195] noted the recovery of a patient with hemolytic streptococcic meningitis of otogenic origin after surgical drainage, frequent spinal taps and administration of convalescent scarlet fever serum, prontosil soluble and sulfanilamide. Lewy [196] treated 8 patients with otogenic meningitis with sulfanilamide or prontosil. Of 6 with positive cultures of the spinal fluid, 3 died. The 3 fatal attacks were due to the hemolytic streptococcus. One patient showed profound changes in the dura and was moribund when therapy was started; 1 may have died because of the lack of specificity of the drug for alpha hemolytic streptococci, but this patient and the third who died seemed benefited by the drugs and lived longer than the average patient with meningitis. In 1 of the cases in which treatment was successful organisms were demonstrated on smear but not on culture. A. Lewy [162] reported the recovery of 4 patients with meningeal extension after mastoiditis when sulfanilamide was given. Smith and Coon [197] reported 2 cases of otogenic meningitis caused by a hemolytic streptococcus in which recovery followed the use of prontosil soluble and sulfanilamide.

Bloch and Pacella [198] reported staphylococcic meningitis in a 17 day old infant who responded favorably to treatment with oral and intrathecal administration of sulfanilamide. Jackson [199] reported recovery in a case of staphylococcic meningitis. Fritz and Hollister [200]

195. Woodman, DeG.: Otitic Meningitis: Report of a Case in Which Treatment Was Followed by Recovery, Arch. Otolaryng. **26**:310 (Sept.) 1937.

196. Lewy, R. B.: The Use of Prontosil and Sulfanilamide in the Treatment of Otogenic Meningitis: Report of Eight Cases, Ann. Otol., Rhin. & Laryng. **46**: 1096 (Dec.) 1937.

197. Smith, H. B., and Coon, E. H.: Meningitis Due to Hemolytic Streptococcus: Report of Two Cases with Recovery After the Use of Prontosil and Sulfanilamide, Arch. Otolaryng. **26**:56 (July) 1937.

198. Bloch, H., and Pacella, B. L.: Staphylococcic Meningitis: Report of a Case in a Seventeen Day Old Infant Successfully Treated with Sulfanilamide, J. A. M. A. **110**:508 (Feb. 12) 1938.

199. Jackson, R. L.: Staphylococcus Aureus Meningitis: Report of Case with Recovery, J. Pediat. **11**:518 (Oct.) 1937.

200. Fritz, M., and Hollister, W.: Meningitis Due to Staphylococcus Aureus Haemolyticus: Report of a Recovery, Arch. Otolaryng. **27**:317 (March) 1938.

treated a patient with otogenic meningitis due to Staph. aureus haemolyticus with staphylococcus antitoxin, blood transfusions and prontosil soluble administered intramuscularly. Recovery occurred, but because of toxic neuritis of both eighth nerves there was complete loss of hearing. In general, there is not much evidence that sulfanilamide offers possibilities of coping with staphylococcic infections. The original prontosil has been noted to have some chemotherapeutic effect, however, in various staphylococcic infections by Schranz,[24] Anselm,[17c] Schreus,[17b] Tonndorf,[201] Meyer zu Hörste [202] and Jaeger.[203] Imhauser [18] reported failure in treating septic conditions in 2 cases, in 1 of which the patient died from meningitis as the result of intracranial foci. Colebrook and Purdie,[130] however, were able to cure 2 of 3 patients with puerperal staphylococcic septicemia. Basman and Perley [104] reported 2 patients with staphylococcic septicemia dying in spite of sulfanilamide therapy.

Pneumococcic Meningitis.—That sulfanilamide is a potent therapeutic agent in experimental pneumococcic infections in animals has been shown by numerous investigators,[204] but the application of the drug to infections in man has not been widespread. Heintzelman, Hadley and Mellon [205] reported 19 cases of type III pneumonia, in which 9 of the patients were treated with sulfanilamide and 10 received no special form of treatment. The drug was administered orally. Seven of 9 treated with the drug recovered and 2 died. Of the 10 untreated patients, 2 recovered and 8 died. In a group of 33 cases not under their direct observation 9 patients recovered and 24 died when the drug was given. The mortality for all patients not treated with sulfanilamide was 74 per cent; that for the treated patients, 22 per cent. Millett [206] reported that the recovery of a patient with type III pneumonia was due to sulfanilamide therapy. Waring and Rettberg [159] obtained poor clinical results in all types of pneumonia, and 1 patient with type V pneumococcic lobar pneumonia died.

Neal and Appelbaum [171] used sulfanilamide in 14 cases of pneumococcic meningitis; 3 patients recovered and 11 died. The fifteenth had

201. Tonndorf, E.: Eine lückenlose Reihe von Erysipelheilungen durch Prontosil, Med. Klin. **32**:1307 (Sept. 18) 1936.

202. Meyer zu Hörste, G.: Zur Prontosilbehandlung, Klin. Wchnschr. **15**: 1602 (Oct. 31) 1936.

203. Jaeger, K. H.: Ueber örtliche Prontosilanwendung, Deutsche med. Wchnschr. **62**:1831 (Nov. 6) 1936.

204. Domagk.[84] Cooper, Gross and Mellon.[40] Hoerlein.[85a] Colebrook and Kenny.[77a] Rosenthal.[86a] Rosenthal, Bauer and Branham.[45] Nitti, Bovet and Depierre.[87] Buttle, Parish, McLeod and Stephenson.[88]

205. Heintzelman, J. H. L.; Hadley, P. B., and Mellon, R. R.: The Use of *p*-Amino-Benzenesulfonamide in Type III Pneumococcus Pneumonia, Am. J. M. Sc. **193**:759 (June) 1937.

206. Millett, J.: Sulfanilamide: Report of a Case, New York State J. Med. **37**:1743 (Oct. 15) 1937.

meningitis caused by a mixed infection with Pneumococcus type III and Str. viridans and died in spite of sulfanilamide therapy. Waring and Rettberg [159] reported 2 deaths from pneumococcic meningitis and 2 deaths from pneumococcic septicemia, although all patients received adequate doses of the drug. Mertins and Mertins [207] reported recovery after treatment with sulfanilamide in a case of unclassified type IV pneumococcic meningitis of otitic origin. Bassman and Perley [104] reported the recovery of a patient with otogenic meningitis caused by infection with type V pneumococci after treatment with sulfanilamide, and the death of a patient with otogenic meningitis caused by infection with type III pneumococci, probably because of inadequate doses. Mitchell and Trachsler [118] reported the recovery of a patient with meningitis caused by infection with type V pneumococci but since ethylhydrocupreine hydrochloride had also been used, he attributed the favorable outcome to that drug rather than to sulfanilamide. Kopetzky [192] described the recovery of a patient with otogenic meningitis due to Pneumococcus type III by means of the removal of a residual bony focus in the zygomatic root of the temporal bone, repeated small transfusions and daily administration of sulfanilamide by mouth.

Other Types of Meningitis.—Basman and Perley [104] were able to culture Bacillus proteus from the spinal fluid and blood of a child with otogenic meningitis. Sulfanilamide was used intrathecally, intramuscularly and orally. Improvement was noted for three days, during which time cultures of the blood and the spinal fluid were negative. The child was worse on the fourth day, and operation on the fifth day revealed a coalescent type of mastoiditis, with cells filled with pus, granulation tissue and débris. Postoperative recovery was uneventful.

McIntosh and others [117] reported 2 cases of meningitis due to H. influenzae in which both the patients died. One patient, whose condition was of otogenic origin, had hemolytic streptococci in the mastoid wound, and H. influenzae was obtained on culture of the blood. Administration of sulfanilamide was started one week after mastoidectomy, but there was no effect on either the hemolytic streptococci or the influenza bacilli. McQuarrie [208] noted improvement in a case of meningitis due to H. influenzae in which both influenza serum and sulfanilamide were given, but after two weeks the patient became progressively worse and died. Hageman [132] treated a patient with influenzal meningitis with sulfanilamide, but the disease ran its natural course and terminated fatally. Basman and Perley [104] were unable to alter

207. Mertins, P. S., and Mertins, P. S., Jr.: Meningitis Due to Type IV Pneumococcus, with Recovery: Report of a Case, Arch. Otolaryng. **25**:657 (June) 1937.

208. McQuarrie, I.: Report of Cases Treated with Sulfanilamide (Prontosil and Prontylin), J. Pediat. **11**:188 (Aug.) 1937.

the course of otogenic meningitis due to H. influenzae with sulfanilamide in 1 case, and the patient died. There is, as yet, little clinical evidence that the drug is of value in influenzal meningitis, but Neal and Appelbaum [171] have reported the recovery of a patient with influenzal meningitis treated with anti-influenzal serum and sulfanilamide. They again emphasized that whenever meningitis is secondary to a focus of infection it is important to eradicate this focus as completely and as promptly as possible.

Meningococcic Meningitis.—Buttle and others [39a] and Proom [74] demonstrated the protective and curative properties of the drug against meningococcic infections in mice. Schwentker, Gelman and Long [145] reported 10 cases of meningococcic meningitis and 1 of septicemia in which sulfanilamide was administered intraspinally and subcutaneously; there was 1 death, of pneumonia on the fifth day, although the spinal fluid was sterile for three days and the cell count was only 158 on the day of death. In some cases, the cell count of the spinal fluid fell rapidly and progressively. In other cases, the count remained elevated for several days and then decreased precipitously. Cultures of the spinal fluid were sterile after the first treatment in a number of cases, and in no instance was the organism recovered later than three days after treatment was begun. Transient arthritis developed in 2 patients. When given subcutaneously, the solution was absorbed and gave rise to no more tenderness or reaction at the site of injection than does physiologic solution of sodium chloride when similarly administered. No signs of local or systemic reaction followed intrathecal injection. The response to treatment was good in every case and seemed comparable to that produced by the specific antiserum. One definite value of the drug over antimeningococcus serum was the absence of any irritation due to foreign protein. McIntosh [117] treated 2 patients with meningococcic meningitis and bacteremia with specific antiserum and sulfanilamide, and both recovered. Mitchell and Trachsler [118] reported the recovery of 3 patients with meningococcic meningitis given combined therapy with antiserum, antitoxin and sulfanilamide administered intraspinally and by mouth. Bernstein [170] and Basman and Perley [104] have each reported 2 cases with recovery. Carey [109] treated 5 patients, 3 of whom had positive cultures of the blood, with the drug alone, and all recovered. Branham [209] reported on the comparative efficacy of serum, antitoxin and drugs in the treatment of meningococcic meningitis. Brennemann [157] was uncertain as to the value of the drug in a case in which the patient recovered but antitoxin also had been used. Willien [210] in 5 cases of meningococcic meningitis found the response satis-

209. Branham, S. E.: Serum, Antitoxin and Drugs in Treatment of Meningococcic Meningitis, M. Ann. District of Columbia **7**:1 (Jan.) 1938.

210. Willien, L. J.: Sulfanilamide Therapy in Meningococcic Meningitis, J. A. M. A. **110**:630 (Feb. 26) 1938.

factory when sulfanilamide alone was administered orally. He pointed out that the possibility of a cure in such cases by oral administration alone is of great practical importance in eliminating the time, trouble and expense of intraspinal and intravenous therapy, the danger of protein shock and the discomfort of serum sickness. He expressed the opinion that $2 worth of the drug might do the work of $500 worth of serum and do it better. Since the drug is bacteriostatic rather than bactericidal, it is important to continue its administration in reduced doses for ten days to two weeks after the symptoms subside and thus prevent recurrences. Arman-Delille and Weill-Halle [211] expressed the belief that the drug is just as effective when given by mouth as when administered parenterally. Two patients with meningitis promptly recovered when treated with sulfanilamide after no improvement had been obtained with polyvalent antimeningococcus serum. Zendel and Greenberg [212] reported 2 cases of meningococcemia in which cures were brought about by the drug. One of the patients, ill with a high fever for seven weeks, who had had three episodes of meningitis and had been treated with large amounts of meningococcic antitoxin and antiserum intravenously, intramuscularly and intrathecally without effect on the infection of the blood stream, had become extremely sensitive to both antitoxin and antiserum. The prompt recovery after treatment with sulfanilamide was striking. Brown, Bannick and Habein [213] have discussed the use of the drug in meningococcic infections and concurred in describing its efficacy.

Abscess of the Brain.—Basman and Perley [104] reported 2 cases of otitic abscess of the brain (in 1 caused by infection with the type III pneumococcus and in 1 by infection with a nonhemolytic streptococcus) with recovery after sulfanilamide therapy.

Cavernous Sinus Thrombosis.—MacNeal and Cavallo [214] reported the recovery of a patient presenting roentgenologic evidence of pansinusitis, with positive cultures of the blood for hemolytic streptococci, severe cyanosis of the face, engorgement of the veins of the forehead and eyelids, marked chemosis of the conjunctivas, including the right cornea, and proptosis on both sides. While the recovery of the patient was the principal evidence against the diagnosis, the clinical picture was that of cavernous sinus thrombosis.

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211. Chemotherapy of Cerebrospinal Meningitis, Foreign Letter (Paris), J. A. M. A. **110**:297 (Jan. 22) 1938.

212. Zendel, J. F., and Greenberg, D.: Meningococcemia: Report of Two Cases, New York State J. Med. **37**:1744 (Oct. 15) 1937.

213. Brown, A. E.; Bannick, E. G., and Habein, H. C.: The Use of Sulfanilamide and Prontosil Solution, Minnesota Med. **20**:691 (Nov.) 1937.

214. MacNeal, W. J., and Cavallo, M. E.: Streptococcic Bacteremia and Apparent Thrombosis of the Cavernous Sinuses with Recovery, J. A. M. A. **109**: 2139 (Dec. 25) 1937.

Bacteremia.—Sulfanilamide appears to be strikingly effective against the types of bacteremia due to the beta hemolytic streptococcus, the meningococcus and, to some extent, the pneumococcus. It is ineffective against Str. viridans and the staphylococcus. Keefer [215] reported 9 cases of hemolytic streptococcic infection with bacteremia, and 8 cases of hemolytic streptococcic infection without bacteremia. All the patients were treated with sulfanilamide. Three died, of whom 1 was comatose and had polyarthritis when treatment was begun, 1 had bronchopneumonia and empyema and another had thrombophlebitis of the right internal jugular vein and submaxillary abscess.

Erysipelas.—The effectiveness of the original prontosil in the treatment of erysipelas was reported in 1935.[216] Similar good results obtained with sulfanilamide and its derivatives have since been reported by various authors.[217] Breen and Taylor [218] used sulfanilamide in 35 cases of erysipelas and were particularly impressed with the results for patients between the ages of 50 and 65. Marzollo [219] administered sulfanilamide to 26 patients, including infants and children, suffering from acute erysipelas. The fever abated and leukocytosis diminished during the first or second day or rarely during the third or fourth day. In 88 per cent of the cases, fever disappeared by crisis and the cutaneous symptom improved as soon as the fever abated. Snodgrass and Anderson [220] found the action of sulfanilamide not to be dramatic but stated

215. Keefer, C. S.: Hemolytic Streptococcus Infections, with Especial Reference to Prognosis and Treatment with Sulfanilamide, New England J. Med. **218**: 1 (Jan. 6) 1938.

216. Gmelin, L.: Zur Chemotherapie des Erysipels im Kindesalter, München. med. Wchnschr. **82**:221 (Feb. 7) 1935. Lampert, J.: Prontosil gegen Erysipel, Zentralbl. f. Chir. **62**:2947 (Dec. 14) 1935. Klee and Römer.[17a] Schreus.[17b] Imhauser.[18] Roth.[23]

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that the patients on whom it was employed showed better results than those treated with ultraviolet radiation or scarlet fever antitoxin. These authors later [221] found that the administration of the drug reduced the incidence of complications and diminished the tendency to recurrence. Fever was rare after forty-eight hours of sulfanilamide therapy, and the lesions failed to spread after the same period. Scherber,[222] Frankl [217c] and Kramer [26] found that the rapid alteration in the clinical course of erysipelas was easier to explain on the basis of neutralization of toxin than on the basis of bactericidal action. Basman and Perley [104] stated that some of their most satisfactory results with sulfanilamide were obtained in cases of erysipelas. They encountered 4 instances of the formation of abscess in their 9 patients. In 1 case, the erysipelas followed antrotomy. Hageman and Blake [137] reported 27 patients with erysipelas treated with sulfanilamide. The duration of the disease in the control group was 13.9 days, as compared to 5.3 days in the group treated with sulfanilamide. Spread of the local lesions was noted in 66 per cent of the control series, while only 11 per cent of those treated showed more than slight marginal spread. Two infants with erysipelas and positive cultures of the blood recovered when treated with sulfanilamide. Watson-Williams [158] obtained good results in 70 cases of erysipelas, bringing about recovery without a single death.

Infection of a Wound.—Some interest attaches to the report of Purdie [223] of a case of chronic infection of a wound due to a hemolytic streptococcus, following puerperal sepsis due to the same organism three years previously. Various operative procedures and actinotherapy had failed to give relief. Oral administration of sulfanilamide and local treatment with the drug sterilized the wound and resulted in complete healing.

Infections of the Sinuses.—There is a singular paucity of reports concerning the effects of sulfanilamide on infections of the sinuses. Watson-Williams [158] reported the drug to be efficacious in treating acute infections of the paranasal sinuses. McIntosh [117] used sulfanilamide in 2 cases of maxillary sinusitis due to the hemolytic streptococcus. In 1 case the drug was given after drainage of both antrums because maxillary and ethmoid sinusitis had been present for six months, but the

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effects of the drug were questionable. In the other case, the patient, with bilateral maxillary sinusitis and recurrent pneumonia of six weeks' duration, was treated conservatively for five weeks. Sulfanilamide was then given for two weeks, and no recurrence of fever followed. Favorable results were also obtained with sulfanilamide in a case of ethmoid sinusitis with orbital cellulitis. Mitchell and Trachsler [118] said that sinusitis was apparently favorably affected by sulfanilamide therapy. Hageman [132] found sinusitis to respond favorably in 4 cases without surgical intervention when the drug was used.

Use of Sulfanilamide in Other Diseases.—Swift, Moen and Hirst [224] concluded that the toxic action of sulfanilamide in cases of active rheumatic fever so far outweighed the beneficial therapeutic effect that its administration to patients with this disease did not seem justified. Recknagel [19] and McQuarrie,[208] however, noted some improvement in cases of acute rheumatic fever. Basman and Perley [104] had inconclusive results in 2 cases of rheumatic fever. Brown and Bannick [225] reported that sulfanilamide had failed in a case of tularemia but had hastened the recovery in a case of acute infectious mononucleosis. McQuarrie [208] obtained no results with sulfanilamide in 2 cases of lymphatic leukemia. McIntosh and others [117] were also unable to demonstrate any beneficial effect of the drug in acute lymphatic leukemia. Bohlman [226] reported 3 cases of post-traumatic gas gangrene, in each of which the condition was associated with compound fractures of the leg or thigh. While the dramatic result in these cases was thought to be due to a specific effect on the gas bacillus, it was admittedly possible that the outcome was due in part to the checking of symbiotic growth with the streptococcus or other aerobes. In 1 case, the temperature became normal and no toxic symptoms appeared eighteen hours after the first dose of sulfanilamide. All 3 patients had received gas gangrene antitoxin without appreciable effect, but Ghormley's contributions [227] on the general value of prophylactic antitoxin cannot as yet be discarded. Bohlman suggested that in all cases involving severe crushing injuries, in which streptococci or gas bacilli may subsequently appear, a combination of antitoxin and sulfanilamide may present the greatest advance in the prevention of gas gangrene infection.

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MORPHOLOGIC AND ROENTGENOLOGIC ASPECTS OF THE TEMPORAL BONE

STUDY OF 536 BONES WITH SPECIAL REFERENCE TO PNEUMATIZATION

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(Concluded from page 580)

CLASSIFICATION OF ADULT MATERIAL

Four examples from the previous section have been selected to represent phases of normal pneumatization. The word phase is used in contradistinction to such a term as stage because it is intended to imply absence of strictly delimiting boundaries. Figure 4 *B* shows the picture at birth; representatives of this phase will henceforth be referred to as group I. Figure 5 *B* shows the normal development one finds at the approximate age of 2 years; representatives of this phase will be referred to as group II. Figure 5 *F* reveals the phase which has extensive pneumatization except in the apex of the pyramid, where there is none; representatives of this phase will hereafter be called group III. Complete pneumatization of the pyramid (cells in the apex) is shown in figure 6 *F*; representatives of this phase show no arrest and henceforth will be group IV.

As an illustration of the method of classification, observe figure 7 *A*, Specimen 1439 R, a bone of a 57 year old white man. By comparison with figure 4 *B*, it is noted that pneumatization has been arrested at birth or even before; thus this bone is classified in group I. Specimen 1726 R (fig. 7 *B*) is that of another 57 year old white man. By comparison with figure 5 *B*, it is seen to show pneumatization which was arrested near the 2 year phase, and is therefore classified in group II. Specimen 1460 R (fig. 7 *C*) is that of a 61 year old man and shows no pneumatization in the apex when compared with figure 5 *F* but is otherwise extensively pneumatized, thus going into group III. Figure 7 *D* is the left side of the specimen 1439, referred to previously in this paragraph, and by comparison with figure 6 *F* shows widespread pneumatization including the apex (no arrest) and is classified in group IV.

Since groups I and II have arrested pneumatization (complete and partial) and groups III and IV show little if any arrest of pneumatiza-

tion (slight arrest and no arrest), I and II would be expected to have many morphologic features in common, especially if the apical or carotid part of the pyramid is not included. In group IV there are bones showing a small amount of pneumatization in the apex and bones which show complete pneumatization of the apex. The morphologic features and mensural data on each temporal bone were recorded before roentgeno-

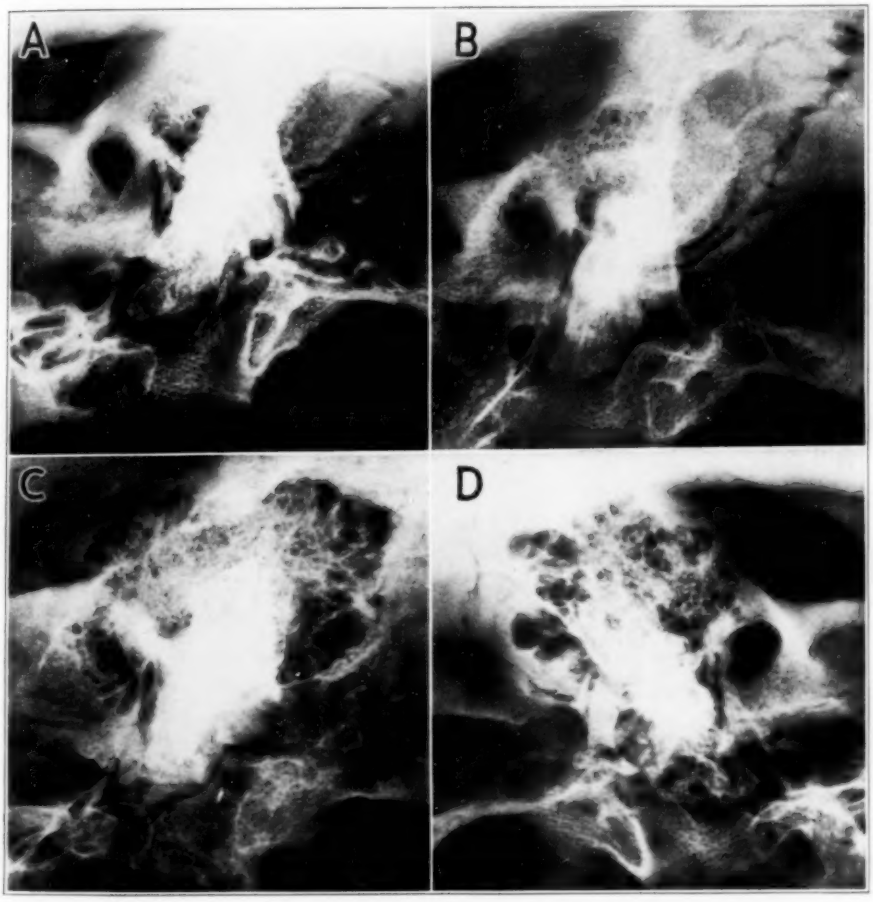

Fig. 7.—*A*, skull 1439 R, white man, age 57. Pneumatization was arrested at birth. *B*, skull 1726, white man, age 57. Pneumatization was arrested in the 2 year phase. *C*, skull 1460, white man, age 61. There is extensive pneumatization except in apex or carotid part of the pyramid. *D*, skull 1439 L, white man, age 57 (fig. 7 *A*). Pneumatization is complete.

grams were made. Accordingly, the data represent an unprejudiced measurement, because at the time of recording them it was not known in which group a bone would finally be classified.

The total anatomic material used in this study comprises the following series of temporal bones:

69 skulls, i. e., 138 bones, ranging in maturation age from 7 fetal months to 15 years. These show no distinguishing sexual or racial characters. They were used in the process of building the standard of development.

39 skulls, i. e., 78 bones, of chronologic age 16 to 20. These also show no distinguishing racial or sexual characters.

50 skulls, i. e., 100 temporal bones, of white men, chronologic age 20 to 30.

50 skulls, i. e., 100 temporal bones, of Negro men, chronologic age 20 to 30.

50 skulls, i. e., 100 temporal bones, of white men, chronologic age 55 to 65.

TABLE 1.—*Skeletal Numbers of 100 Temporal Bones of 55 to 65 Year Old White Men Classified into Groups I to IV* *

I	II			III	IV
1439 R	1726 R & L	899 R	1206 R & L	1460 R & L	1439 L
1280 R & L	1588 R & L	1943 R & L	1210 R & L	1488 R & L	1013 R & L
1770 R & L	554 L	906 R & L	1872 R & L	1553 R & L	1492 R & L
1236 R & L	1019 L	621 R & L	1504 R & L	1026 R	1026 L
1061 R & L	1669 R & L	869 R & L	1011 R & L	1458 R & L	1514 R & L
1347 R & L	1564 R & L	1591 R & L	1741 R & L	1382 R & L	
554 R	1033 R & L	1058 R & L	1570 R & L	995 R & L	
1019 R	991 R	912 R & L	1217 R & L	1203 R & L	
899 L	1486 R & L	923 R & L	797 R & L	1685 R & L	
991 L	1764 R & L	1745 R & L	1255 R & L	1472 R & L	
				1167 R & L	

* R = right; L = left—indicating individual temporal bones.

In addition, 20 temporal bones were studied before and after maceration; therefore, the aggregate is 536 temporal bones.

The series of specimens of 55 to 65 year old white men definitely represents a stage at which no further development of pneumatization need have been expected in those particular temporal bones; it may be said that in examining them one is examining the final result. The bones falling into groups I, II, III and IV, according to the roentgenologic classification herein developed, were tabulated separately (table 1), and for each group the measurements and features A, B, C through L were listed (tables 2, 3, 4 and 5). These measurements and features have already been defined. In this series of 100 bones of 55 to 65 year old white men, 15 show arrest at birth; 56 show arrest at or near the 2 year period of development; 21 show arrest only in the sense that no cells were formed in the apex, and 8 show complete pneumatization

(cells in apex). It is interesting to observe that in specimen 1439 the right side shows arrest at birth and the left side no arrest at all (fig. 7 *A* and *D*). This is an excellent example of the wide differences which may be found on the two sides of one skull. Seventy-one, namely the total number included in groups I and II, show arrest from some factor in early life; of the 29, i. e., groups III and IV together, which escaped this factor in early life, only 8 bones show complete freedom from arrest somewhere in life.

In considering each of the four groups in this series, one should refer to tables 2, 3, 4 and 5. In group I (arrest at birth) the distance (A) between the depression of Wilde and the arcuate eminence averages

TABLE 2.—*Group I from Table 1, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
1439 R	23.0	32.0	3.5	10.0	14.0	15.0	16.0	18.0	4.0 × 11.0	35	High ○	14.0
1280 R	24.0	32.5	3.5	7.0	11.0	9.5	11.0	17.0	16.0 × 6.0	50	High ○	13.0
1280 L	23.0	35.0	4.5	6.0	12.0	8.5	16.0	20.0	10.0 × 6.0	45	High ○	10.0
1770 R	24.0	33.0	4.0	9.5	16.0	13.0	22.0	19.0	3.0 × 15.0	35	Low —	17.0
1770 L	22.0	32.0	4.0	9.5	15.0	11.0	19.0	15.5	5.0 × 14.0	40	Medium ○	11.0
1236 R	23.0	30.0	5.0	8.0	14.5	12.5	23.0	22.0	4.0 × 10.0	40	Low —	12.0
1236 L	23.0	30.5	4.0	8.0	13.5	12.0	23.5	19.0	5.0 × 12.0	30	High ○	7.0
-1061 R	26.0	32.5	2.0	6.0	15.5	13.0	17.0	22.0	4.0 × 11.0	35	Medium ○	14.0
1061 L	28.0	31.5	3.0	7.0	15.5	13.0	15.0	21.0	13.0 × 3.0	20	High ○	11.0
1347 R	24.0	34.0	3.0	8.5	13.0	11.5	16.0	16.0	5.0 × 15.0	40	High ○	12.0
1347 L	24.0	34.0	5.0	8.0	14.5	12.0	15.0	18.0	5.0 × 11.0	20	High ○	11.0
554 R	30.0	39.0	3.0	7.5	9.5	9.5	17.0	21.0	5.0 × 7.5	20	High ○	11.0
1019 R	21.0	33.5	2.5	6.0	13.5	13.0	19.0	19.0	5.0 × 15.0	20	Medium —	11.0
899 L	24.0	31.5	3.5	7.5	12.0	13.5	16.0	19.0	16.0 × 7.0	30	High ○	7.0
991 L	22.0	34.5	4.0	6.5	13.0	13.0	13.0	21.0	8.0 × 15.5	55	High ○	11.0
Maximum	30.0	39.0	5.0	10.0	16.0	15.0	23.5	22.0				17.0
Minimum	21.0	30.0	2.0	6.0	9.5	8.5	11.0	15.5				7.0
Average	24.0	33.0	3.6	7.7	13.5	12.0	17.2	19.2				11.5

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

24.0 mm. (15 bones) and ranges from 21.0 to 30.0 mm. In group II the same distance averages 23.7 mm. and ranges from 20.0 to 27.0 mm. In group III the average (A) is 25.8 mm. and the range from 22.5 to 29.0 mm. Group IV, which shows no arrest, has an average of 26.2 mm. and a range from 24.0 to 28 mm. From this comparison it is noticed that the distance between the two landmarks under consideration is less in groups I and II, which show arrest in early life, than in groups III and IV, which escape arrest in early life.

For the distance (B) between the arcuate eminence and the medial tip of the apex of the pyramid, the average of group I is 33.0 mm., group II 33.3 mm., group III 34.3 mm. and group IV 32.8 mm. The maximum and minimum measurements can be found in the tables. For the sake of brevity, only the averages will be considered, among which

TABLE 3.—*Group II from Table 1, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
1588 R	23.0	30.0	2.0	6.5	11.0	12.5	13.0	21.5	6.0 × 12.0	45	High ○	14.0
1588 L	23.0	32.5	2.0	6.0	12.5	12.0	14.0	21.0	13.5 × 6.0	55	High ○	13.0
1726 R	23.0	32.5	3.0	8.0	12.0	9.0	20.0	16.0	4.0 × 12.0	55	Low —	11.0
1726 L	22.0	37.5	3.5	6.5	12.0	10.0	16.0	13.0	6.0 × 13.0	60	High ○	13.0
554 L	26.0	34.0	3.0	7.5	9.5	9.5	14.0	17.0	5.0 × 13.5	45	High ○	12.0
1019 L	23.0	32.5	3.0	6.5	11.0	11.0	20.0	20.0	3.0 × 15.5	20	Medium —	14.0
1669 R	21.0	34.0	2.5	6.0	12.5	13.5	17.0	20.0	14.0 × 5.0	50	High ○	14.0
1669 L	23.0	36.5	3.5	6.5	12.0	9.5	17.0	17.5	12.5 × 5.0	45	High ○	12.5
1564 R	23.0	33.0	3.0	9.0	13.0	10.0	21.0	17.0	5.0 × 16.0	50	Medium ○	13.5
1564 L	23.0	30.0	3.5	9.0	12.0	9.5	18.0	17.5	15.5 × 4.0	40	Medium —	14.0
1033 R	24.0	32.0	3.5	7.5	14.0	12.0	22.0	18.0	2.0 × 10.0	35	Low —	10.0
1033 L	26.0	32.0	3.0	9.0	15.0	13.0	20.0	17.0	4.0 × 11.0	60	Low —	10.0
991 R	21.0	35.0	4.0	8.0	12.5	14.0	15.0	18.0	5.0 × 13.0	40	High ○	15.0
1486 R	24.0	36.0	3.5	9.5	15.0	13.5	21.0	18.5	3.0 × 3.0	40	Medium —	19.0
1486 L	25.0	32.5	3.0	9.5	15.0	14.0	22.5	18.0	1.0 × 6.0	45	Low —	21.0
1764 R	20.0	26.0	3.5	7.5	12.5	11.0	15.0	18.5	5.0 × 7.0	35	High ○	12.0
1764 L	23.0	32.0	3.0	6.0	13.5	10.0	21.5	17.0	15.0 × 6.0	40	Low —	14.0
899 R	22.0	32.5	2.5	8.0	11.5	16.5	15.5	20.0	6.0 × 17.0	30	High ○	11.0
1943 R	22.0	35.0	2.0	9.0	13.5	10.0	17.0	18.0	5.5 × 20.0	40	High ○	11.0
1943 L	23.0	32.0	2.0	9.0	14.0	10.5	21.0	22.0	18.0 × 6.0	50	Low —	12.0
996 R	26.0	30.5	5.0	7.5	15.0	12.0	22.5	22.0	6.0 × 13.5	25	Low —	17.0
996 L	26.5	29.0	4.0	9.0	15.0	13.0	19.0	21.0	4.0 × 13.0	40	High ○	15.0
621 R	22.0	32.0	1.5	7.0	14.0	12.5	16.0	19.0	5.0 × 14.0	55	High ○	12.0
621 L	24.0	32.0	2.0	7.5	15.5	14.0	15.0	18.0	6.0 × 15.0	45	High ○	16.0
869 R	21.0	31.5	2.0	7.0	15.0	11.0	17.0	16.5	4.0 × 13.0	40	High ○	13.0
869 L	25.0	33.0	3.0	6.5	14.5	12.0	17.0	19.0	3.0 × 8.0	40	High ○	15.5
1591 R	24.0	36.0	3.5	7.5	15.0	14.5	19.0	19.0	5.0 × 21.0	25	High ○	15.0
1591 L	24.0	32.5	3.5	9.0	12.0	13.5	14.0	16.0	4.0 × 20.0	40	High ○	12.0
1058 R	26.0	30.5	3.0	8.0	14.5	10.0	19.0	17.0	12.5 × 4.0	25	Medium —	12.0
1058 L	26 0	29.0	4.0	8.0	15.5	10.0	23.5	20.0	11.5 × 4.0	30	Low —	12.0
912 R	27.0	36.0	6.0	6.0	13.5	12.0	15.0	20.0	5.0 × 10.0	25	High ○	11.0
912 L	26.0	34.0	6.0	6.5	13.0	13.0	19.5	19.5	5.0 × 6.0	35	Low —	9.0
923 R	26.0	32.5	2.5	8.5	11.5	12.0	20.5	22.5	5.0 × 10.0	40	High —	21.0
923 L	26.0	31.0	3.5	8.5	13.0	14.0	17.0	21.0	4.0 × 12.0	45	Medium ○	19.0
1745 R	23.0	38.0	5.0	7.5	14.0	13.0	17.0	14.0	5.0 × 17.0	45	Medium ○	16.5
1745 L	26.0	35.0	4.5	6.5	13.0	13.5	22.0	16.0	3.0 × 11.0	45	Low —	19.0
1206 R	24.0	33.0	3.0	7.0	14.0	14.0	14.0	19.0	5.0 × 14.0	55	High ○	20.0
1206 L	24.5	34.0	3.0	7.5	15.0	16.0	20.0	18.0	6.0 × 10.0	50	Low —	15.0
1210 R	23.0	38.0	3.0	7.0	13.5	11.0	21.0	16.0	5.0 × 17.0	30	Medium —	11.0
1210 L	23.0	37.0	2.5	7.0	15.0	12.5	23.5	20.0	5.0 × 9.0	40	Low —	11.0
1872 R	22.5	32.0	4.0	8.5	11.0	15.5	12.0	17.5	3.0 × 4.0	50	High ○	14.0
1872 L	24.0	36.5	3.0	7.0	11.5	12.5	19.0	18.5	5.0 × 8.0	40	Low —	10.0
1504 R	25.0	33.0	2.5	7.0	12.0	13.5	14.0	19.0	4.0 × 9.0	40	High ○	15.0
1504 L	26.0	33.0	2.0	7.0	12.0	11.5	17.0	18.5	5.0 × 12.0	30	Medium ○	12.5
1011 R	25.0	35.0	2.5	6.0	11.5	13.0	15.5	18.0	3.0 × 14.0	60	High ○	13.0
1011 L	24.0	37.0	2.5	6.5	11.5	12.0	16.0	18.0	3.0 × 15.0	50	High ○	16.0
1741 R	21.0	32.5	2.0	6.0	14.0	10.0	22.0	21.0	9.0 × 8.0	40	Low —	14.0
1741 L	22.0	32.0	3.0	7.0	13.0	12.0	17.0	18.0	5.0 × 10.0	45	Medium ○	15.0
1570 R	22.0	35.0	1.5	8.0	13.0	9.5	18.0	21.0	5.5 × 10.5	50	Medium ○	20.0
1570 L	23.0	35.0	2.0	9.0	14.0	11.0	12.0	20.0	6.0 × 13.0	40	High ○	16.0
1217 R	23.0	33.5	3.5	7.0	15.0	14.0	13.0	19.5	8.0 × 16.0	50	High ○	15.0
1217 L	22.0	33.5	4.5	7.0	13.5	15.0	15.0	19.5	8.0 × 18.0	40	Medium —	14.0
797 R	24.0	36.0	3.0	6.0	14.0	10.0	12.0	18.0	4.0 × 19.0	35	High ○	11.0
797 L	25.0	38.0	3.0	6.0	14.5	9.0	17.0	21.0	6.0 × 14.0	30	High ○	13.0
1255 R	22.0	31.5	3.5	5.5	12.5	11.0	15.5	17.5	5.5 × 19.0	35	High ○	12.0
1255 L	23.0	29.0	4.0	5.5	12.0	10.0	20.0	19.0	7.0 × 16.0	35	Low —	10.0
Maximum	27.0	37.5	6.0	9.5	15.5	16.5	23.5	22.5				21.0
Minimum	20.0	26.0	1.5	5.5	9.5	9.0	12.0	13.0				9.0
Average	23.7	33.3	3.1	7.4	13.2	12.0	17.6	18.6				13.9

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

the extreme difference to be found is only 1.5 mm. In other words, this dimension is fairly constant under all conditions once adult life is reached. In the thickness (C) of the roof of the internal auditory canal there are considerable individual differences, but the averages are

TABLE 4.—*Group III from Table 1, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
1488 R	23.0	31.5	3.0	6.0	12.0	13.0	18.0	21.0	12.5 × 7.0	50	Medium ○	17.0
1488 L	24.0	32.0	2.5	7.5	12.5	13.5	19.0	21.5	6.0 × 18.5	35	Low —	16.0
1553 R	28.0	35.0	3.0	7.5	13.5	15.0	13.0	17.0	8.0 × 14.0	45	High ○	16.0
1553 L	27.0	34.0	3.0	7.5	14.5	18.0	22.0	21.0	6.0 × 10.5	50	Medium —	18.0
1026 R	27.0	32.5	5.0	11.0	16.0	16.5	16.0	20.0	2.0 × 9.0	35	High ○	18.0
1460 R	26.0	30.5	4.5	9.0	13.5	13.0	14.0	16.0	4.0 × 8.5	30	High ○	18.0
1460 L	26.0	30.0	6.0	10.0	11.5	13.0	17.0	22.0	0	30	High ○	21.0
1458 R	25.0	31.5	3.0	10.0	14.5	11.0	21.5	22.0	6.0 × 11.0	55	Low —	15.0
1458 L	22.5	37.0	3.5	11.5	16.0	9.5	17.0	25.0	9.0 × 5.0	60	High ○	23.0
1382 R	24.0	34.0	3.0	4.5	14.5	15.5	21.5	19.0	6.0 × 16.0	35	Low —	11.0
1382 L	23.0	38.0	2.5	4.0	11.5	13.0	21.0	16.5	8.0 × 11.0	50	Low —	10.5
995 R	26.0	36.0	5.0	7.5	16.5	9.5	25.0	16.5	5.0 × 7.0	40	Medium —	15.0
995 L	27.0	38.5	4.5	10.0	15.0	14.0	23.5	16.0	5.0 × 11.5	45	Medium —	14.0
1203 R	25.0	35.0	2.5	7.5	13.0	13.0	20.0	17.0	5.0 × 23.0	50	Medium —	16.0
1203 L	27.0	35.5	3.0	8.0	12.0	15.0	20.5	16.0	4.0 × 20.0	45	Medium ○	14.0
1685 R	28.0	34.0	3.0	8.0	12.0	14.5	20.0	18.0	6.0 × 15.0	45	Low —	17.0
1685 L	26.0	35.0	4.0	7.5	13.0	14.5	19.0	15.0	6.0 × 13.0	30	Low —	18.0
1472 R	26.0	32.5	5.0	8.0	14.5	11.0	13.0	16.0	4.5 × 8.0	20	High ○	17.0
1472 L	28.0	32.0	3.0	7.0	15.0	10.5	20.0	22.0	8.0 × 8.0	20	Medium —	17.0
1167 R	29.0	36.0	5.0	9.0	15.0	12.0	15.0	20.0	11.5 × 6.0	40	High ○	11.0
1167 L	28.0	39.0	5.0	9.0	14.0	14.0	19.0	20.0	11.5 × 4.0	40	Medium —	13.0
Maximum	29.0	39.0	6.0	11.5	16.5	18.0	25.0	25.0				23.0
Minimum	22.5	30.0	2.5	4.0	11.5	9.5	13.0	15.0				10.5
Average	25.8	34.3	3.8	8.1	13.8	13.3	18.8	18.9				16.0

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

TABLE 5.—*Group IV, from Table 1, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
1439 L	27.0	31.0	2.0	13.0	15.0	17.0	16.0	18.0	5.0 × 10.5	40	High ○	15.0
1013 R	25.0	31.5	3.0	7.0	16.5	14.0	17.0	18.0	7.0 × 3.0	20	High ○	13.0
1013 L	24.0	30.0	3.0	9.0	13.0	15.0	15.0	17.0	3.0 × 13.0	20	High ○	13.0
1492 R	26.0	35.0	3.0	8.5	16.0	12.0	23.5	22.0	6.0 × 15.0	45	Low —	16.5
1492 L	28.0	34.0	3.0	7.5	13.5	11.5	11.0	20.0	7.0 × 10.0	40	High ○	19.0
1026 L	26.0	31.0	6.5	11.5	16.0	12.0	14.0	21.5	2.0 × 1.0	35	High ○	17.0
1514 R	26.0	37.0	4.0	8.0	15.0	14.0	23.5	23.0	8.0 × 22.0	45	Low —	17.0
1514 L	28.0	33.5	4.0	10.0	14.0	14.0	13.0	21.0	6.0 × 21.0	20	High ○	24.0
Maximum	28.0	37.0	6.5	13.0	16.5	17.0	23.5	22.0				24.0
Minimum	24.0	30.0	2.0	7.0	13.0	11.5	11.0	17.0				13.0
Average	26.2	32.8	3.5	9.3	14.8	13.7	16.6	20.0				16.8

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

much alike. The average distance (D) from the internal carotid artery to the posterior surface of the pyramid in the midapical area increases from 7.7 mm. in group I to 9.3 mm. in group IV.

The position of the hiatus Fallopii measured from the posterior edge of the pyramid (F) is farther forward in group IV (13.7 mm.) than in

group I (12.0 mm.). The minimal distance from the jugular fossa to the top of the arcuate eminence (G) increases from 17.2 mm. in group I to 17.6 mm. in group II and to 18.8 mm. in group III and then decreases to 16.6 mm. in group IV. The relation of the anterior margin of the lateral sinus to the arcuate eminence, it is true, shows considerable range, but the averages of the four groups show no significant differences. Again, while the osseous dehiscence over the internal carotid artery shows considerable variation, there is no significance in the statistically

TABLE 6.—*Skeletal Numbers of 100 Temporal Bones of 20 to 30 Year Old White Men Classified into Groups I to IV**

I	II				III	IV
436 R & L	267 R & L	484 R & L	680 R & L	623 R & L	712 R & L	583 R & L
628 L	688 R & L	1327 R & L	94 R & L	1546 R & L	1160 R & L	667 R & L
614 R & L	1769 R & L	1612 R & L	2584 R & L	1393 R & L	2565 R & L	2041 R & L
341 R & L	1163 R & L	310 R & L	694 R & L	1039 R & L	360 R & L	423 R & L
1043 R & L	628 R	2192 R & L	471 R & L	469 R & L	575 R & L	1298 R
238 R & L	1298 L	2454 R & L	490 R	1674 R & L	424 R	503 R & L
	958 R & L	215 R & L	672 R & L	643 R & L	687 R & L	
	376 R & L	424 L	618 R & L	392 R & L	490 L	
	1873 R & L	288 R & L				

* R = right; L = left—indicating individual temporal bones.

TABLE 7.—*Group I from Table 6, with Individual Data Listed**

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
436 R	24.0	26.0	3.0	4.0	12.0	8.5	13.5	16.5	6.0 × 10.0	60	High ○	8.0
436 L	24.0	35.0	3.0	5.0	12.0	11.0	14.0	21.0	6.0 × 12.5	60	High ○	8.0
628 L	21.0	32.0	2.5	7.5	10.0	7.5	13.0	16.0	6.0 × 7.0	20	High ○	9.0
614 R	23.0	34.5	2.0	10.5	11.5	13.5	15.0	17.0	3.5 × 8.0	35	High ○	12.0
614 L	24.0	31.0	3.0	10.0	14.0	12.0	17.0	21.5	3.5 × 8.0	40	High ○	18.0
341 R	20.0	35.5	4.0	6.5	13.0	12.0	17.0	16.0	4.0 × 10.5	50	High ○	10.0
341 L	20.5	33.0	4.0	6.5	14.5	14.0	16.5	17.0	3.0 × 9.0	50	High ○	13.0
1043 R	21.0	35.0	6.0	7.5	13.0	12.0	19.0	16.5	4.0 × 9.0	20	Medium ○	15.0
1043 L	26.0	32.0	6.0	8.5	14.5	11.5	20.0	18.5	6.0 × 11.0	20	Low —	13.0
238 R	25.0	33.0	2.5	7.0	12.0	8.5	19.5	20.5	4.0 × 13.0	40	Medium ○	12.0
238 L	25.0	32.0	3.5	6.0	13.5	7.0	15.5	19.5	3.5 × 13.5	35	High ○	11.0
Maximum	26.0	36.0	6.0	10.5	14.5	14.0	20.0	21.5				18.0
Minimum	20.0	31.0	2.0	4.0	10.0	7.0	13.0	16.5				8.0
Average	23.0	33.5	3.6	7.2	12.7	10.7	16.4	18.2				11.7

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

reduced data. To this statement, however, specimen 1460 L presents an exception, for it has no bony dehiscence (1 only out of the 100 bones).

It is to be noticed that in specimen 899 L the angle formed by the posterior root of the zygoma as it turns up from the plane of the zygomatic arch is 30 degrees (J) and the minimal distance from the lateral sinus to the depression of Wilde (L) is 7.7 mm. Again, specimen 1236 L has an angle of 30 degrees with a distance of 7.7 mm., whereas in specimen 991 L there is an angle of 50 degrees and the distance is 11 mm., and specimen 1770 R has an angle of 35 degrees with a distance of

TABLE 8.—*Group II from Table 6, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
267 R	22.0	36.0	2.5	6.5	15.0	11.0	14.0	18.0	5.0 × 8.5	20	High ○	9.0
267 L	22.0	37.5	4.0	6.5	12.5	9.5	23.0	21.5	4.0 × 9.0	20	Low —	13.5
688 R	19.0	34.5	3.5	7.5	12.0	9.0	16.5	17.0	5.0 × 12.5	40	Medium —	14.0
688 L	20.5	35.0	3.0	7.5	13.0	10.0	17.0	15.5	4.5 × 10.0	30	Medium —	12.0
1769 R	22.0	31.5	5.5	7.5	13.0	11.5	18.5	16.0	11.5 × 5.0	50	Medium —	12.0
1769 L	26.0	28.5	5.0	7.5	15.0	13.5	20.5	24.5	13.5 × 6.0	50	Low —	15.0
1163 R	23.0	33.0	5.0	8.0	13.0	11.5	19.0	17.0	10.0 × 7.0	45	Medium ○	17.0
1163 L	23.0	32.5	4.0	7.5	14.0	11.0	20.5	18.5	13.0 × 7.0	40	Medium —	17.0
628 R	20.0	35.0	2.5	8.0	11.5	8.0	16.0	16.0	5.0 × 9.0	25	Medium —	13.0
1298 L	22.0	31.5	3.5	6.0	16.5	10.5	16.0	19.0	4.0 × 17.0	20	High ○	11.5
958 R	20.0	36.0	4.0	8.0	12.5	11.5	16.5	22.0	5.0 × 11.0	40	High ○	17.0
958 L	21.0	35.5	4.0	9.5	14.5	19.0	16.0	18.5	4.5 × 10.0	55	High ○	13.0
376 R	21.0	37.0	4.0	5.5	12.5	9.5	22.0	19.5	6.0 × 11.0	45	Low —	14.0
376 L	20.0	36.5	5.0	7.0	14.0	11.5	19.0	17.0	12.5 × 6.0	45	Medium ○	13.0
1873 R	21.5	29.5	3.0	7.5	12.5	10.0	18.0	18.0	4.5 × 9.0	35	High ○	12.0
1873 L	21.0	29.5	2.0	8.0	13.0	13.5	20.0	21.5	6.0 × 12.0	30	High —	11.0
484 R	24.0	32.0	5.0	9.0	13.0	11.5	16.0	18.5	2.0 × 3.0	25	High ○	11.0
484 L	26.0	31.5	6.0	10.0	13.5	12.5	14.0	20.0	2.0 × 3.0	35	High ○	13.0
1327 R	20.0	35.0	4.0	6.0	14.0	7.5	23.0	21.5	3.0 × 7.0	45	Low —	17.0
1327 L	20.0	35.5	3.5	5.5	12.0	9.0	16.0	15.5	4.0 × 11.5	50	High ○	13.0
1612 R	23.0	36.5	4.5	7.0	17.0	12.5	15.0	18.0	5.0 × 8.0	45	High ○	18.0
1612 L	23.0	37.5	4.0	8.0	14.0	12.0	22.0	22.5	5.0 × 8.0	25	Low —	14.0
310 R	25.0	35.0	3.5	6.0	12.5	11.0	20.0	22.0	5.0 × 10.0	20	High —	12.0
310 L	25.0	33.5	3.0	8.0	12.5	10.0	21.0	20.5	6.0 × 12.0	45	Medium —	9.0
2192 R	23.0	33.0	2.5	6.0	15.0	11.0	16.5	18.5	0	25	High ○	11.0
2192 L	24.0	34.5	3.0	8.0	16.5	17.0	14.5	17.0	4.0 × 7.0	35	High ○	8.5
2454 R	22.5	37.5	2.5	5.5	12.5	12.0	17.0	18.0	5.0 × 7.0	30	High ○	12.0
2454 L	23.0	33.5	2.5	6.0	13.5	11.5	15.0	17.5	4.5 × 4.0	30	High ○	12.0
215 R	22.5	35.5	4.5	10.0	17.0	11.5	24.0	18.0	4.0 × 13.5	40	Medium —	15.0
215 L	22.0	36.0	4.0	8.0	17.5	9.5	22.0	17.5	4.5 × 14.0	35	High —	11.0
288 R	24.0	35.5	4.0	8.0	14.0	10.0	21.5	21.0	5.0 × 10.5	25	High ○	12.0
424 L	25.0	38.0	4.5	8.5	12.5	10.0	22.5	16.5	5.0 × 10.5	20	Low —	15.0
288 L	24.0	34.5	3.5	7.5	15.0	10.0	20.5	19.0	4.0 × 11.0	25	High ○	12.0
680 R	22.0	38.0	4.0	8.5	11.5	12.5	24.0	15.5	5.0 × 5.0	20	Low —	16.0
680 L	27.0	30.5	4.0	8.5	13.0	13.5	19.0	22.0	2.0 × 2.0	20	Low —	17.5
94 R	25.0	38.0	3.0	5.0	16.0	10.0	19.5	18.0	4.0 × 18.5	45	High —	14.0
94 L	26.0	36.5	3.5	6.0	13.0	12.0	17.0	20.5	4.5 × 17.0	40	Medium ○	19.0
2584 R	25.0	33.5	4.0	7.0	13.5	13.0	17.0	19.0	5.5 × 11.0	40	Medium ○	17.0
2584 L	26.0	34.5	3.5	7.0	14.0	12.0	21.5	12.5	5.0 × 8.0	35	Low —	24.0
694 R	19.0	37.5	2.5	6.5	10.5	10.0	19.0	14.5	6.0 × 7.0	30	Low —	13.0
694 L	21.5	37.0	3.0	7.0	12.0	12.0	18.5	12.5	5.0 × 9.5	20	Low —	8.0
471 R	20.0	35.0	3.0	7.0	13.5	9.0	15.0	17.0	6.0 × 9.5	70	High ○	15.0
471 L	22.0	36.0	3.5	7.0	14.0	10.5	22.0	19.0	9.0 × 6.0	45	Low —	15.0
490 R	22.0	35.0	4.0	8.0	15.0	13.5	15.0	11.5	1.0 × 3.0	30	High ○	9.0
672 R	20.0	39.0	2.7	8.0	11.5	10.5	24.5	17.0	10.0 × 4.0	35	Low —	16.0
672 L	25.0	33.0	3.5	9.5	13.0	10.5	16.0	15.5	4.0 × 6.0	25	High ○	11.0
618 R	21.0	36.0	2.5	7.5	12.0	8.5	15.0	13.5	6.0 × 10.0	45	High ○	18.0
618 L	21.0	35.5	3.0	7.0	12.5	9.5	20.0	17.0	7.0 × 13.0	35	Medium ○	11.0
623 R	24.0	35.5	3.0	8.5	15.5	10.0	18.5	21.0	7.0 × 14.0	20	High ○	16.0
623 L	26.0	38.0	2.5	8.5	14.0	10.0	18.0	19.0	5.0 × 13.0	30	High ○	13.0
1546 R	23.0	33.5	4.0	9.5	15.0	10.5	14.0	17.5	5.0 × 10.0	30	High ○	17.0
1546 L	24.0	33.5	4.5	9.0	15.0	12.0	16.0	21.0	4.0 × 10.5	35	High ○	14.0
1393 R	26.0	36.0	1.0	7.0	10.0	11.0	14.0	18.5	3.0 × 7.0	35	High ○	15.5
1393 L	24.0	35.0	1.0	6.0	10.5	12.0	14.0	17.5	3.5 × 11.0	35	High ○	16.0
1039 R	22.0	31.5	3.5	6.5	13.0	8.0	16.5	17.5	6.0 × 6.0	40	High ○	13.0
1039 L	23.0	34.5	3.0	6.0	12.5	9.0	16.5	15.0	7.0 × 18.0	20	High —	9.0
469 R	22.0	34.5	3.0	6.5	12.5	11.0	15.0	15.5	5.0 × 8.0	20	High ○	11.0
469 L	23.0	35.5	3.5	7.0	13.5	13.0	16.0	14.5	3.0 × 16.0	25	High ○	12.5
1674 R	23.0	36.5	4.0	7.5	15.0	11.0	20.0	27.0	5.0 × 9.0	45	High ○	15.0
1674 L	23.0	39.0	4.0	7.0	15.0	10.0	22.0	20.5	5.0 × 12.0	35	High —	15.0
643 R	22.0	35.0	3.0	7.0	15.0	10.5	14.0	14.0	4.0 × 5.0	40	High ○	17.0
643 L	23.0	37.0	3.0	6.0	14.0	9.5	17.0	15.5	1.0 × 3.0	45	High ○	16.0
392 R	27.0	35.0	3.7	8.5	12.5	16.0	16.0	23.0	4.5 × 10.5	35	High ○	19.0
392 L	24.0	40.5	3.7	9.5	13.0	16.5	18.0	20.0	4.0 × 14.0	35	High ○	19.0
Maximum	27.0	40.5	6.0	10.0	17.5	19.0	24.5	27.0				24.0
Minimum	19.0	29.5	1.0	5.0	10.0	7.5	14.0	11.5				8.0
Average	22.8	35.0	3.5	7.4	13.6	11.2	18.1	18.2				13.9

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

17.0 mm. From these examples it is obvious that a small angle (J) does not necessarily imply a long distance (L) nor a great angle a short distance. The angulation of the posterior root of the zygoma, therefore, possesses no clinical significance even for group I, in regard to which its

TABLE 9.—*Group III from Table 6, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
712 R	27.0	41.0	3.0	8.0	15.0	14.5	18.0	19.0	3.0 × 2.0	35	High ○	19.0
712 L	27.0	42.5	3.0	8.0	15.5	15.0	17.0	17.5	2.0 × 8.5	25	High ○	17.0
1160 R	20.0	32.0	3.5	7.0	11.0	13.0	16.0	26.0	7.0 × 6.5	20	High ○	21.0
1160 L	25.0	34.0	4.0	7.5	13.0	15.5	20.0	21.5	6.0 × 7.5	35	Medium ○	22.0
2565 R	23.0	35.0	2.5	7.0	12.0	10.5	17.0	22.5	4.5 × 15.5	20	High —	18.0
2565 L	27.0	34.0	2.5	8.0	14.5	10.5	12.0	19.0	5.0 × 16.5	20	High ○	14.0
360 R	24.0	40.0	3.0	8.0	11.0	12.0	24.5	11.5	6.0 × 14.5	40	Low —	16.0
360 L	26.0	33.0	4.0	6.0	13.0	9.5	16.0	18.0	5.0 × 14.0	40	High ○	14.0
575 R	22.0	32.5	3.0	8.0	11.0	14.0	17.0	19.0	5.0 × 9.5	25	High ○	15.0
575 L	24.0	32.5	3.0	8.0	13.0	12.0	22.5	17.5	3.0 × 4.0	25	Low —	15.0
424 R	24.0	36.0	5.0	8.0	13.5	11.5	21.0	19.5	4.0 × 10.0	20	Low —	20.5
687 R	26.0	36.0	4.0	10.5	14.0	17.0	23.5	19.0	4.5 × 18.0	35	Medium —	20.0
687 L	26.0	33.0	4.5	11.0	13.5	15.0	24.5	19.5	3.0 × 2.0	40	Medium —	20.5
490 L	24.0	34.0	4.0	7.0	13.5	13.5	17.5	18.0	4.5 × 7.0	45	High ○	13.0
Maximum	27.0	42.5	5.0	11.0	15.5	17.0	24.5	26.0				22.0
Minimum	20.0	32.0	2.5	7.0	11.0	9.5	16.0	11.5				13.0
Average	24.6	35.5	3.5	8.0	13.1	13.1	19.0	19.1				17.5

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

TABLE 10.—*Group IV from Table 6, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
583 R	22.0	34.0	4.5	10.0	14.5	14.5	22.5	23.0	6.0 × 10.0	35	Low —	16.0
583 L	24.0	30.0	5.5	9.5	15.0	13.0	19.0	18.0	8.0 × 7.0	40	Medium ○	12.0
667 R	25.0	33.0	4.0	7.0	13.5	15.5	24.0	18.5	8.0 × 7.0	20	Low —	14.0
667 L	24.0	32.5	5.0	7.5	16.5	16.0	20.0	18.0	6.0 × 10.0	35	Medium ○	14.0
2041 R	25.0	38.0	3.0	6.5	12.0	11.0	18.0	17.5	7.0 × 9.0	40	High —	20.0
2041 L	29.0	35.5	3.0	6.5	12.0	13.5	23.5	19.0	2.5 × 18.0	40	Low —	19.0
423 R	25.0	36.0	4.0	7.5	14.5	11.5	19.0	15.0	5.5 × 7.0	20	Low —	16.0
423 L	26.0	36.5	4.0	8.0	14.0	13.5	22.0	18.5	6.0 × 11.0	25	Low —	19.0
1298 R	22.0	32.5	3.0	5.0	15.5	9.5	20.0	17.5	6.0 × 20.0	35	High ○	12.0
503 R	22.0	39.0	5.5	9.0	16.0	13.5	24.0	18.5	5.0 × 11.0	40	Low —	20.0
503 L	26.0	36.0	6.0	7.5	16.0	13.5	26.0	21.0	6.0 × 7.5	25	Low —	16.0
Maximum	29.0	39.0	6.0	10.0	16.5	16.0	26.0	23.0				20.0
Minimum	22.0	30.0	3.0	5.0	12.0	9.5	18.0	15.0				12.0
Average	24.5	34.8	4.3	7.6	14.5	13.2	21.6	18.6				16.2

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

meaning might have been expected to be most significant in surgery. As Wittmaack [2] has said, the forward position of the lateral sinus occurs only in pathologic pneumatization. Returning to the dimension (L) between the lateral sinus and the depression of Wilde, one finds a gradual increase from 11.5 mm. in group I to 13.9 mm. in group II, to 16.0 mm. in group III and to 16.8 mm. in group IV. The significance

of this is that the bones which are free from arrest naturally show inflation and therefore a larger dimension than the bones in which pneumatization was arrested in early life.

In a more general way specimens from this series of bones of 55 to 65 year old men may be compared with a series of men of 20 to 30 years. It is a striking and significant fact that the morphologic features

TABLE 11.—*Skeletal Numbers of 100 Temporal Bones of 20 to 30 Year Old Negro Men Classified into Groups I to IV* *

I	II		III		IV
1699 R & L	855 R & L	1092 R & L	2203 L	874 R & L	2203 R
1312 R & L	809 R	859 R & L	2009 R & L	862 R & L	1201 R & L
970 R	970 L	959 L	1072 R & L	782 R & L	857 R & L
1361 R & L	792 R & L	1233 R	778 R & L	1204 R & L	1360 R & L
1084 R & L	1014 R & L	1094 R	791 R & L	1086 R & L	846 R & L
1372 R & L	1134 R & L	569 R & L	716 R & L	1112 L	858 L
	1054 R & L	2281 R & L	1360 R & L	703 L	1112 R
	1141 R & L	1967 R & L	1044 R & L	959 R	
	703 R	568 R & L	809 L	1233 L	
	941 R & L	2060 R & L	1278 R & L	1094 L	
	860 R & L	1957 R & L	1742 R & L		
	858 R	1682 R & L			
	1442 R & L				

* R = right; L = left—indicating individual temporal bones.

TABLE 12.—*Group I from Table 11, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
1699 R	19.0	34.0	3.0	7.5	10.0	12.5	14.0	13.0	5.0 × 8.0	35	High —	7.0
1699 L	21.0	31.0	4.0	8.0	11.0	13.5	15.5	15.5	3.0 × 11.0	45	Medium —	8.0
1312 R	20.0	34.0	2.0	4.0	9.0	11.0	15.0	20.0	5.0 × 11.0	45	High ○	6.0
1312 L	20.0	36.5	2.5	4.0	10.5	11.0	14.0	14.5	3.0 × 10.0	50	High ○	3.5
970 R	18.0	32.5	5.0	8.5	15.0	10.0	15.0	16.5	2.0 × 7.0	35	High ○	8.0
1361 R	21.5	35.0	2.0	6.5	11.0	12.0	17.0	22.0	5.0 × 10.0	55	Medium ○	9.0
1361 L	22.0	35.5	2.5	6.0	11.0	14.0	12.0	19.0	5.0 × 11.0	45	High ○	6.0
1084 R	21.0	35.0	4.5	7.0	12.0	13.5	17.0	14.5	5.0 × 12.0	45	High ○	13.0
1084 L	22.0	35.5	3.0	8.5	11.5	13.5	16.5	16.0	4.0 × 8.0	40	High ○	9.0
1372 R	19.0	38.0	4.0	8.0	11.0	13.0	15.5	16.0	7.0 × 11.0	50	Medium ○	6.0
1372 L	21.0	36.5	3.5	9.5	11.0	14.0	16.0	16.5	7.0 × 11.0	40	Medium —	5.5
Maximum	22.0	38.0	5.0	9.5	15.0	14.0	17.0	22.0				13.0
Minimum	18.0	31.0	2.0	4.0	9.0	10.0	12.0	13.0				3.5
Average	20.4	34.9	3.2	7.0	11.2	12.5	15.2	16.7				7.3

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

(A through L) of the bones of younger men, when the corresponding groups of the two series are compared, show no significant difference in average measurement. To inquire what part, if any, racial stock plays in these data, one may compare the series of bones of 20 to 30 year old white men with the specimens from 20 to 30 year old Negro men. The two present identical numbers of bones under headings group I and group IV. When groups II and III are added together (and it must be admitted that there is often considerable difficulty in assign-

ment to one or the other of these groups), the two series again present identical numbers. More bones from the white men (compare groups II of the various series) show development arrested early in life as compared with those from Negroes. It may be that the Negro escapes

TABLE 13.—*Group II from Table 11, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
855 R	23.0	33.0	3.5	7.5	11.0	11.0	16.0	17.0	7.0 × 10.0	50	Medium ○	9.0
855 L	21.0	35.0	5.0	7.5	10.0	10.0	16.0	17.5	5.0 × 14.0	35	Medium ○	10.0
809 R	25.0	37.5	3.5	10.5	13.0	15.0	15.0	16.5	6.0 × 7.0	45	High ○	12.0
970 L	20.0	32.0	4.5	7.0	12.5	11.0	17.5	16.5	3.0 × 11.0	30	Medium ○	10.0
792 R	22.0	37.0	3.0	7.0	12.0	16.0	17.5	22.0	5.0 × 8.0	35	High ○	13.0
792 L	25.0	34.5	3.5	7.5	12.5	15.5	17.0	21.5	4.0 × 9.0	40	High ○	11.0
1014 R	22.0	33.0	3.0	8.5	10.5	13.0	14.0	21.0	7.0 × 7.0	50	High ○	11.0
1014 L	23.0	31.0	4.0	8.5	10.0	13.5	19.0	20.0	5.0 × 5.0	40	Low —	10.5
1134 R	24.0	38.0	3.5	10.5	14.0	11.5	15.0	18.0	7.0 × 10.0	40	High ○	6.0
1134 L	24.0	39.5	4.5	10.0	13.5	13.0	21.0	21.0	11.0 × 8.0	55	Low —	8.0
1054 R	20.0	34.0	4.0	6.0	12.0	19.0	17.0	15.0	5.0 × 14.0	40	Medium ○	11.0
1054 L	21.0	35.5	3.5	7.5	12.0	9.5	18.5	17.0	5.0 × 11.0	40	Medium ○	10.5
1141 R	21.0	35.0	4.5	8.5	16.0	10.5	16.0	19.0	10.0 × 4.0	60	High ○	11.0
1141 L	19.0	36.5	4.5	10.0	16.0	11.0	24.0	24.0	4.0 × 13.0	60	Low —	12.0
703 R	24.0	35.0	6.0	8.0	13.5	14.0	21.0	16.5	5.0 × 12.0	45	Low —	14.0
941 R	23.0	33.0	4.5	9.5	14.0	13.0	20.0	22.0	3.0 × 5.0	40	Low —	15.0
941 L	25.0	32.0	5.0	10.0	13.0	12.5	13.0	18.0	2.0 × 3.0	50	High ○	16.0
860 R	24.0	36.0	4.0	5.0	11.0	11.5	20.0	24.0	1.0 × 3.0	20	Low —	11.0
860 L	24.0	35.0	4.5	4.0	11.0	13.0	17.0	18.0	4.0 × 14.0	20	Medium ○	6.0
858 R	18.0	40.0	3.0	8.0	11.0	10.0	18.0	18.5	0	25	Medium —	11.0
1442 R	22.5	35.0	4.5	6.0	12.0	13.0	12.5	17.0	7.0 × 9.0	50	High ○	14.0
1442 L	25.0	35.0	6.0	7.0	14.0	14.0	24.0	22.0	6.0 × 7.0	45	Low —	12.0
1092 R	23.0	32.5	6.0	8.5	14.5	15.0	19.0	17.5	0	40	Medium ○	13.0
1092 L	24.0	34.0	7.5	9.0	15.0	16.5	19.5	16.0	0	50	Medium ○	14.0
859 R	21.5	35.0	4.0	6.5	13.0	10.5	15.5	19.0	6.0 × 7.0	30	High ○	16.0
859 L	22.0	34.5	3.0	5.0	12.0	11.0	20.0	19.0	3.0 × 11.5	25	Low —	14.0
959 L	24.0	33.0	4.5	10.0	13.0	16.5	12.0	19.0	2.0 × 3.0	35	High ○	10.0
1233 R	26.0	38.0	4.0	10.0	15.0	17.0	22.5	27.0	4.0 × 6.0	55	Low —	16.0
1094 R	24.0	33.0	4.5	8.0	11.5	13.0	15.5	17.0	3.0 × 5.0	40	Medium —	10.0
569 R	22.0	35.0	5.0	8.5	12.0	11.5	21.5	20.0	6.0 × 10.0	40	Low —	9.0
569 L	18.0	41.0	5.0	9.0	12.5	15.5	16.0	13.5	4.0 × 14.0	40	High ○	10.0
2281 R	22.0	32.0	1.5	3.5	13.0	10.5	16.0	22.0	6.0 × 14.0	50	Medium ○	14.0
2281 L	23.0	30.5	1.0	5.0	14.0	12.5	19.0	19.0	5.0 × 14.0	40	Low —	16.0
1967 R	27.0	39.5	2.0	7.0	12.0	12.5	18.5	19.5	4.0 × 9.0	40	Medium ○	17.0
1967 L	24.0	38.5	2.5	8.0	12.0	12.5	14.0	18.0	4.0 × 9.0	55	High ○	17.0
568 R	25.0	36.0	2.0	8.0	11.0	13.0	20.5	17.0	4.0 × 11.0	35	Low —	10.0
568 L	27.0	36.0	3.0	8.5	11.0	13.5	24.0	23.0	4.0 × 14.0	50	Low —	16.0
2060 R	25.0	40.0	1.5	8.5	11.0	15.5	16.5	16.0	3.0 × 6.0	50	High ○	9.0
2060 L	24.0	37.5	2.0	9.0	15.0	16.0	19.0	18.0	7.0 × 10.0	40	Low —	9.0
1957 R	20.0	34.0	3.5	6.0	10.0	14.5	20.0	17.0	4.0 × 15.0	40	Low —	11.5
1957 L	20.5	33.0	4.0	6.5	11.0	15.0	18.0	18.0	4.0 × 16.0	50	Medium ○	10.0
1682 R	23.0	34.0	4.0	8.0	13.0	15.5	14.0	19.0	5.0 × 11.0	50	High ○	12.0
1682 L	24.0	34.0	4.0	7.0	12.0	12.0	22.0	23.0	3.0 × 12.0	35	Low ○	14.0
Maximum	27.0	41.0	7.5	10.5	16.0	19.0	**24.0**	27.0				17.0
Minimum	18.0	30.5	1.0	4.0	10.0	9.5	12.0	13.5				6.0
Average	22.9	35.2	3.9	7.8	12.5	13.3	18.0	19.0				11.9

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

the retarding influence more than the white person during this phase of life, or else more of those afflicted die in childhood. In the morphologic features (A through L), one finds no significant differences between the races. Hence, from the standpoint of structure and of

TABLE 14.—*Group III from Table 11, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
2203 L	26.0	33.0	3.5	9.0	15.0	14.5	20.5	19.0	5.0 × 13.0	35	Low —	20.0
2009 R	20.0	39.0	4.5	7.0	13.0	13.5	15.5	11.0	5.0 × 15.0	30	High ○	14.0
2009 L	24.0	33.0	4.0	6.0	12.5	13.0	18.0	17.0	5.0 × 18.0	35	Low —	15.0
1072 R	23.0	30.0	5.0	8.0	14.0	13.0	18.0	16.5	2.0 × 3.0	35	Medium ○	14.0
1072 L	24.0	31.5	4.5	8.5	13.0	12.5	20.5	16.5	3.0 × 5.0	35	Low —	16.0
778 R	27.0	35.0	6.0	10.0	16.0	15.0	21.5	16.0	0	35	Low —	19.0
778 L	26.5	36.0	7.0	9.0	17.0	13.5	27.0	18.5	0	35	Low —	18.0
791 R	24.0	35.0	5.0	6.5	13.0	13.5	17.0	16.0	5.0 × 7.0	30	High ○	14.0
791 L	28.0	33.0	5.0	7.0	12.5	14.0	19.5	18.0	7.0 × 7.0	35	Low —	15.0
716 R	24.0	39.5	6.0	7.5	13.0	14.5	17.0	16.0	3.0 × 11.0	55	High ○	17.0
716 L	27.0	40.0	6.0	8.0	15.5	16.0	21.5	17.0	5.0 × 13.0	55	Low —	17 0
1360 R	25.0	36.0	4.0	9.0	12.0	15.0	21.0	21.5	0	35	Low —	18.0
1360 L	25.0	35.5	5.0	6.0	13.0	16.0	18.0	19.5	6.0 × 4.0	20	Medium ○	16.0
1044 R	24.0	32.0	5.5	9.0	13.5	12.0	18.0	16.0	0	35	Low —	10.0
1044 L	24.0	33.5	5.5	8.0	14.0	13.5	19.5	17.0	0	35	Low —	9.5
809 L	23.0	41.0	5.0	11.0	14.0	10.5	19.0	18.0	4.0 × 6.0	45	Medium ○	14.0
1278 R	25.0	36.0	3.0	7.5	12.0	15.5	21.5	16.0	3.0 × 12.0	20	Low —	14.0
1278 L	26.5	36.0	3.0	8.0	13.0	14.0	18.0	17.0	3.0 × 11.0	20	Medium ○	14.0
1742 R	26.0	34.5	4.5	10.5	12.0	18.0	16.0	20.0	4.0 × 11.0	25	Medium ○	14.0
1742 L	28.0	36.0	6.0	10.5	13.5	18.5	18.0	23.0	4.0 × 7.0	25	Medium —	11.5
874 R	25.0	34.0	3.0	8.5	15.5	14.5	22.5	15.0	0	20	Low —	17.0
874 L	28.0	34.5	3.0	8.0	15.0	13.0	22.0	10.0	2.0 × 4.0	40	Low —	17.5
862 R	25.0	36.0	4.0	8.0	14.0	17.0	17.0	19.0	6.0 × 9.0	60	Medium ○	18.5
862 L	24.5	34.5	4.0	9.0	16.5	13.0	21.0	20.0	6.0 × 7.0	55	Low —	16.0
782 R	25.0	39.0	5.0	8.5	12.0	14.5	20.0	19.5	16.0 × 6.0	30	High ○	19.0
782 L	27.0	37.0	4.5	9.5	12.5	14.0	24.0	21.5	6.0 × 17.0	40	Low —	16.0
1204 R	22.0	39.0	5.0	8.0	12.0	13.0	20.0	14.5	2.0 × 2.0	25	Medium ○	16.5
1204 L	23.0	40.0	5.5	10.0	15.0	16.0	21.0	15.0	5.0 × 4.0	35	Medium —	18.0
1086 L	27.0	30.5	3.5	8.0	13.0	13.5	12.0	21.0	3.0 × 3.0	40	High ○	13.0
1112 L	21.0	30.5	5.0	8.0	11.5	12.0	18.5	14.5	4.0 × 6.0	50	Low —	12.0
703 L	25.0	38.0	5.0	6.5	15.0	13.0	22.5	18.0	4.0 × 12.0	60	Low —	15.0
959 R	25.0	34.0	5.5	11.0	15.5	13.5	21.5	22.5	4.0 × 10.0	35	Low —	14.0
1233 L	26.0	36.0	5.5	9.0	15.0	19.0	17.0	21.5	0	55	High ○	17.0
1094 L	21.0	36.0	4.5	7.0	11.5	13.0	18.0	16.0	6.0 × 9.0	50	Medium ○	14.0
1086 R	24.0	32.0	3.5	9.5	11.0	15.0	16.0	22.0	5.0 × 6.0	40	High ○	12.0
Maximum	28.0	41.0	7.0	11.0	17.0	19.0	27.0	23.0				20.0
Minimum	20.0	30.0	3.0	6.0	11.0	10.5	12.0	10.0				9.5
Average	24.8	35.3	4.7	8.4	13.6	14.3	19.3	17.7				15.3

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

TABLE 15.—*Group IV from Table 11, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
2203 R	24.0	31.5	3.0	8.0	14.0	12.5	20.0	17.0	5.0 × 12.0	50	Low —	15.0
1201 R	26.0	35.0	4.0	8.0	13.5	13.5	20.5	20.5	5.0 × 5.0	30	Low —	19 0
1201 L	26.0	37.0	3.0	8.0	14.0	10.0	23.0	14.0	7.0 × 7.0	25	Low —	17.0
857 R	25.0	35.0	5.0	11.5	15.5	16.5	21.0	21.5	5.0 × 7.0	50	Low —	13.0
857 L	25.0	32.0	5.0	11.0	16.5	15.0	23.0	22.0	3.0 × 4.0	40	Low —	15.0
1360 R	24.0	38.0	4.0	11.0	12.0	16.0	13.0	18.0	0	20	High ○	15.0
1360 L	23.0	37.0	4.5	10.0	11.5	11.0	22.0	19.5	0	20	Low —	14.0
846 R	29.0	38.0	5.0	9.0	12.0	16.0	20.5	17.0	3.0 × 5.0	40	Low —	18.0
846 L	29.0	35.5	4.5	9.0	12.0	15.0	20.0	19.0	7.0 × 9.0	35	Medium —	18.0
858 L	22.0	33.0	2.0	11.5	14.5	9.5	16.0	23.0	0	20	High ○	12.0
1112 R	21.0	30.0	5.0	8.5	11.5	14.0	16.0	16.0	1.0 × 2.0	50	High ○	12.0
Maximum	29.0	38.0	5.0	11.5	16.5	16.5	23.0	23.0				19.0
Minimum	21.0	30.0	2.0	8.0	11.5	9.5	13.0	14.0				12.0
Average	24.9	34.7	4.1	9.6	13.4	13.5	19.5	18.9				15.3

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

TABLE 16.—*Skeletal Numbers of 78 Temporal Bones of Persons 16 to 20 Years Old Classified into Groups I to IV*

I	II		III		IV	
696 R	1228 R & L	291 R & L	1140 L	576 R & L	639 R & L	1232 R & L
693 R & L	1140 R	1040 R & L	563 R & L	410 R & L	588 R	519 R & L
1606 R & L	17 R & L	1589 R & L	548 L	2558 R & L	955 L	854 R
2796 R	1328 R & L	1974 R & L	588 L	854 L	964 L	527 R & L
	696 L	1949 R & L	964 R	2796 L	1012 R & L	807 R & L
	1590 R & L	1707 R & L	1109 R & L	721 R & L	1097 R & L	955 R
	2065 R & L	1339 R & L			2104 R & L	548 R
	1704 R & L	695 R & L				
	1575 R & L					

* No distinction has been made as to color or sex. R = right; L = left—indicating individual temporal bones.

TABLE 17.—*Group I from Table 16, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
696 R	18.0	33.0	5.0	7.0	17.0	11.0	19.0	16.5	12.5 × 3.0	65	High ○	12.0
693 R	20.0	35.0	3.5	6.0	10.0	13.0	18.0	12.5	6.0 × 17.0	50	High ○	15.0
693 L	21.0	34.0	3.0	6.0	10.0	14.0	19.0	16.5	3.0 × 14.0	50	Medium —	15.0
1606 R	22.0	33.0	4.0	7.5	12.0	14.0	14.0	18.0	9.0 × 4.0	25	High ○	11.0
1606 L	22.0	34.0	5.0	9.0	13.0	15.0	14.0	20.0	10.0 × 4.0	55	High ○	9.0
2796 R	22.0	32.5	4.0	10.0	13.5	10.5	21.0	22.0	7.0 × 11.0	20	Medium —	13.0
Maximum	22.0	35.0	5.0	10.0	17.0	15.0	19.0	22.0				15.0
Minimum	18.0	32.5	3.0	6.0	10.0	10.0	14.0	12.0				9.0
Average	20.8	33.6	4.1	7.6	12.6	12.9	17.5	17.6				12.5

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

TABLE 18.—*Group II from Table 16, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
1228 R	22.0	36.0	4.5	8.5	16.5	13.5	17.0	19.0	6.0 × 7.0	35	High ○	17.0
1228 L	26.0	32.0	5.0	8.5	17.0	15.0	18.0	20.0	6.0 × 7.0	40	High ○	17.0
1140 R	28.5	35.0	5.5	9.0	13.0	14.0	20.0	23.0	5.0 × 7.0	45	High ○	15.0
17 R	23.0	34.0	3.0	8.0	11.0	12.0	15.0	17.0	7.0 × 4.0	20	High ○	6.0
17 L	24.0	35.0	2.5	7.0	11.0	13.0	14.0	13.5	6.0 × 3.0	20	High ○	11.0
1328 R	26.0	28.0	4.0	9.0	11.5	14.5	13.0	16.5	3.0 × 7.0	60	High ○	15.0
1328 L	25.0	30.0	5.0	8.0	11.0	14.0	20.0	17.0	2.0 × 3.0	55	Low —	15.0
696 L	19.0	29.5	5.0	8.0	15.0	13.0	21.0	15.0	1.0 × 7.0	55	Medium —	10.0
1590 R	21.0	36.0	3.0	9.0	13.5	14.5	17.0	19.0	5.0 × 3.0	20	Medium —	11.0
1590 L	20.0	38.0	2.5	8.0	11.0	14.5	16.5	22.0	5.0 × 5.0	20	Medium —	14.0
2065 R	24.0	28.5	3.5	8.5	10.5	15.0	16.5	22.0	2.0 × 3.0	40	Medium —	11.0
2065 L	24.0	27.5	4.0	9.0	10.5	16.5	13.0	21.0	1.0 × 1.0	40	High ○	8.0
1704 R	24.0	34.0	3.5	9.0	12.0	15.0	18.0	18.0	6.0 × 8.5	35	Medium ○	13.0
1704 L	24.0	35.0	5.0	11.0	11.5	17.5	19.0	18.0	7.0 × 6.0	45	Medium —	15.0
1575 R	25.0	35.5	4.5	8.5	12.0	13.0	18.0	20.0	6.0 × 12.5	55	Medium —	14.0
1575 L	24.0	37.5	5.0	8.5	11.0	12.0	16.5	16.5	8.0 × 6.0	50	Medium ○	14.0
291 R	20.0	35.0	5.0	8.5	13.0	11.5	19.0	18.0	16.0 × 7.0	20	High —	10.0
291 L	22.0	37.0	4.0	8.0	13.5	11.5	24.0	19.0	6.0 × 16.0	20	Low —	13.0
1040 R	21.0	33.0	3.0	8.0	10.0	15.0	17.0	16.0	3.0 × 6.0	30	High ○	10.0
1040 L	20.0	33.5	3.0	7.0	11.0	14.5	18.0	22.0	3.0 × 4.0	45	Medium ○	12.0
1589 R	24.0	33.0	3.0	7.0	11.0	11.0	19.0	22.0	3.0 × 8.0	30	Medium —	12.0
1589 L	23.0	31.0	3.0	9.0	12.0	11.0	18.0	18.0	6.0 × 8.0	30	Medium —	9.0
1974 R	25.0	31.5	5.0	9.0	13.0	17.5	20.0	20.0	4.0 × 7.0	30	Medium —	13.0
1974 L	26.0	33.0	3.0	9.0	13.0	17.5	21.5	21.0	3.0 × 8.0	35	Medium —	14.0
1949 R	26.0	34.5	6.0	8.0	17.0	17.0	15.5	21.5	1.0 × 3.0	45	High —	15.0
1949 L	24.0	33.0	5.5	8.0	13.0	17.0	15.5	22.0	0	50	High ○	16.0
1707 R	22.0	33.0	3.0	6.0	12.0	11.5	18.0	22.0	15.0 × 4.0	40	Low —	13.0
1707 L	22.0	33.0	4.0	6.5	12.0	11.5	18.5	21.0	4.0 × 12.5	25	Low —	13.5
1339 R	28.0	34.5	3.5	6.5	10.5	13.0	15.0	18.0	6.0 × 8.0	30	High ○	2.0
1339 L	26.0	35.0	3.5	7.0	11.0	13.0	20.5	20.0	6.0 × 8.0	25	Low —	7.0
695 R	29.0	37.0	3.0	9.0	14.0	8.5	15.5	24.0	1.0 × 1.0	20	High ○	10.0
695 L	27.0	35.0	4.0	9.0	11.5	9.5	14.0	22.0	1.0 × 2.0	45	High ○	11.0
Maximum	29.0	38.0	6.0	11.0	17.0	17.5	24.0	24.0				17.0
Minimum	19.0	27.5	2.5	6.0	10.0	8.5	13.0	13.5				2.0
Average	23.9	33.5	4.0	8.2	12.4	13.7	17.5	19.5				12.1

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

TABLE 19.—*Group III from Table 16, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
1140 L	29.0	34.5	5.0	8.0	15.0	13.0	24.5	23.0	4.0 × 5.0	40	Low —	16.5
563 R	23.0	31.5	3.0	8.0	11.0	15.0	15.0	17.0	1.0 × 2.0	35	High ○	15.0
563 L	22.0	33.5	4.0	6.0	12.0	11.0	19.5	16.5	1.0 × 3.0	40	Medium —	13.5
548 L	23.5	35.0	5.0	8.0	12.0	12.5	22.0	21.5	1.0 × 6.0	25	Low —	17.0
588 L	26.0	31.0	3.0	9.0	15.0	11.0	20.0	20.0	5.0 × 7.0	20	Low —	8.0
964 R	24.0	36.5	3.0	6.0	11.0	14.0	17.0	17.5	6.0 × 12.0	35	High —	10.0
1109 R	20.0	34.0	2.5	6.0	10.5	12.0	18.0	16.0	5.0 × 11.0	60	Medium —	13.0
1109 L	21.0	34.0	3.0	6.0	13.0	13.0	20.0	17.0	6.0 × 16.0	60	Medium —	12.0
576 R	26.0	32.0	4.5	8.5	13.0	12.5	21.0	23.5	4.0 × 6.0	20	Low —	13.0
576 L	26.0	32.5	3.5	9.5	12.5	14.0	14.0	19.0	3.0 × 8.0	30	High ○	12.0
410 R	24.0	36.0	4.0	8.0	14.0	11.0	20.0	19.0	5.0 × 11.0	45	Low —	12.0
410 L	26.0	35.0	3.0	8.0	13.0	12.5	13.0	21.0	13.0 × 5.0	40	High ○	12.0
2558 R	23.0	38.0	4.0	6.0	16.0	12.0	20.0	20.0	9.0 × 5.0	50	High ○	15.0
2558 L	24.0	38.0	5.0	6.0	16.0	13.0	21.5	17.0	4.0 × 6.0	50	Low —	20.0
854 L	27.0	31.5	4.0	9.5	11.5	13.5	17.0	18.0	5.0 × 6.0	50	Medium —	15.0
2796 L	26.0	32.0	4.5	10.5	15.0	14.0	23.0	20.5	12.0 × 5.0	40	Low —	15.0
721 R	26.0	37.0	4.5	9.0	13.5	13.5	22.0	21.0	4.0 × 6.0	40	Low —	17.0
721 L	27.0	31.5	4.0	9.0	14.0	12.0	15.0	18.0	9.0 × 4.0	20	High ○	17.0
Maximum	29.0	38.0	5.0	10.5	16.0	15.0	24.5	23.5				20.0
Minimum	20.0	31.0	2.5	6.0	10.5	11.0	13.0	16.0				8.0
Average	24.6	34.1	3.9	7.8	13.2	12.8	19.0	19.2				14.0

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

TABLE 20.—*Group IV from Table 16, with Individual Data Listed* *

Specimen	A	B	C	D	E	F	G	H	I	J	K	L
639 R	27.0	31.0	8.0	9.0	18.0	17.0	26.0	23.0	5.0 × 5.0	20	Low —	20.0
639 L	28.0	30.0	7.5	11.0	17.5	17.0	25.5	25.0	6.0 × 6.0	40	Low —	19.0
588 R	27.0	33.0	4.0	8.5	16.0	13.0	24.0	17.0	5.0 × 8.0	20	Low —	11.0
955 L	24.0	33.0	6.0	7.0	12.0	14.0	21.0	16.0	4.0 × 4.0	40	Low —	15.0
964 L	23.0	33.0	4.0	6.0	16.0	12.0	15.0	17.0	12.0 × 6.0	35	High ○	11.0
1012 R	25.0	29.5	4.5	11.0	12.5	16.0	13.0	19.0	1.0 × 6.0	45	High —	13.0
1012 L	25.0	30.0	4.5	9.0	12.0	17.0	18.0	18.5	3.0 × 4.0	45	High ○	16.0
1097 R	23.0	36.0	3.5	9.0	14.0	14.0	16.0	15.5	4.0 × 6.0	20	High ○	14.0
1097 L	24.0	34.5	4.0	10.5	13.0	12.0	20.0	16.0	3.0 × 6.0	20	Medium —	14.5
2104 R	24.0	26.0	4.0	9.5	10.0	13.5	16.0	19.0	4.5 × 4.0	60	Medium —	12.0
2104 L	21.0	26.0	4.0	8.5	12.0	13.0	20.0	21.0	4.0 × 6.0	65	Low —	12.0
1232 R	25.0	33.0	4.0	11.0	13.5	16.0	19.0	22.0	0	20	Medium —	19.0
1232 L	28.0	33.0	4.0	9.5	15.0	16.5	17.0	21.0	0	20	Medium —	14.0
519 R	24.0	31.0	5.5	12.0	14.0	15.0	17.5	21.0	1.0 × 4.0	30	High ○	21.0
519 L	25.0	30.5	6.5	11.5	15.0	16.0	16.0	20.0	8.0 × 5.0	45	High ○	15.0
854 R	27.0	29.5	3.0	9.0	12.0	11.0	19.5	20.0	3.0 × 4.0	50	Low ○	17.0
527 R	22.0	29.0	4.5	9.5	12.0	10.5	21.0	20.0	5.0 × 10.0	20	Medium ○	12.0
527 L	21.0	27.5	4.0	11.0	12.5	10.0	20.0	21.5	6.0 × 10.0	45	Low —	18.0
807 R	26.0	31.0	5.5	9.5	13.0	15.0	23.0	24.0	1.0 × 1.0	30	Low —	10.0
807 L	25.0	34.0	6.0	9.0	13.0	14.5	15.0	20.0	4.0 × 9.0	40	High ○	10.0
955 R	23.0	31.0	4.0	8.0	12.0	15.0	19.0	16.5	4.0 × 11.0	45	Low —	17.0
548 R	24.0	37.0	4.5	9.0	11.5	13.5	13.0	17.5	1.0 × 3.0	25	High ○	16.0
Maximum	28.0	37.0	8.0	12.0	18.0	17.0	26.0	25.0				21.0
Minimum	21.0	26.0	3.0	6.0	10.0	10.0	13.0	16.0				10.0
Average	24.6	31.3	4.8	9.5	13.5	14.2	18.7	19.6				14.8

* All measurements are recorded in millimeters. Any angle listed in column J as 20 degrees measured 20 degrees or less. The sign ○ is used in column K to indicate roundness of the jugular fossa and the sign — to indicate flatness.

pneumatization, there are no racial distinctions. There were 78 specimens in the series representing the ages from 16 to 20. Though it falls short of the conventional biologic sample of 100, it is the largest series of specimens of which the case histories are known that has been available so far for a scientific study of adolescents. Among these 78 bones (no racial discrimination being made), 22 belong to group IV. It is remarkable that the percentage of bones showing apical pneumatization

TABLE 21.—*Adult Material (378 bones) Divided into Groups I-IV with Average Measurements and Number of Cases of Each Series Listed* *

	No. of Cases	A	B	C	D	E	F	G	H	L
Group I										
55 to 65 yr., men	15	24.0	33.0	3.6	7.7	13.5	12.0	17.2	19.2	11.5
20 to 30 yr., white men	11	23.0	33.5	3.6	7.2	12.7	10.7	16.4	18.2	11.7
20 to 30 yr., Negro men	11	20.4	34.9	3.2	7.0	11.2	12.5	15.2	16.7	7.3
16 to 20 yr	6	20.8	33.6	4.1	7.6	12.6	12.9	17.5	17.6	12.5
Group II										
55 to 65 yr., men	56	23.7	33.3	3.1	7.4	13.2	12.0	17.6	18.6	13.9
20 to 30 yr., white men	64	22.8	35.0	3.5	7.4	13.6	11.2	18.1	18.2	13.9
20 to 30 yr., Negro men	43	22.9	35.2	3.9	7.8	12.5	13.3	18.0	19.0	11.9
16 to 20 yr	32	23.9	33.5	4.0	8.2	12.4	13.7	17.5	19.5	12.1
Group III										
55 to 65 yr., men	21	25.8	34.3	3.8	8.1	13.8	13.3	18.8	18.9	16.0
20 to 30 yr., white men	14	24.6	35.5	3.5	8.0	13.1	13.1	19.0	19.1	17.5
20 to 30 yr., Negro men	35	24.8	35.3	4.7	8.4	13.6	14.3	19.3	17.7	15.3
16 to 20 yr	18	24.6	34.1	3.9	7.8	13.2	12.8	19.0	19.2	14.0
Group IV										
55 to 65 yr., men	8	26.2	32.8	3.5	9.3	14.8	13.7	16.6	20.0	16.8
20 to 30 yr., white men	11	24.5	34.8	4.3	7.6	14.5	13.2	21.6	18.6	16.2
20 to 30 yr., Negro men	11	24.9	34.7	4.1	9.6	13.4	13.5	19.5	18.9	15.3
16 to 20 yr	22	24.6	31.3	4.8	9.5	13.5	14.2	18.7	19.6	14.8

* All measurements are recorded in millimeters.

TABLE 22.—*Weighted Averages of Adult Material**

	No. of Cases	A	B	C	D	E	F	G	H	L
Group I	43	22.42	33.71	3.59	7.37	12.58	11.93	16.53	18.06	10.62
Group II	195	23.27	34.31	3.56	7.61	13.03	12.29	17.86	18.71	13.26
Group III	88	25.03	34.83	4.11	8.15	13.50	13.54	19.11	18.52	15.56
Group IV	52	24.90	33.01	4.36	9.09	13.88	13.75	19.20	19.29	15.52

* All measurements are recorded in millimeters.

should be so large in this sample. There is not even any significant difference in morphologic features from the two previously described series.

The 378 adult temporal bones classified in tables 1, 6, 11 and 16 comprise a total of 43 specimens in group I, 195 specimens in group II, 88 specimens in group III and 52 specimens in group IV. The computed averages for the morphologic features presented by each group in each series are collectively arranged in table 21. The weighted aver-

ages appear in table 22. From these tables (21 and 22) the various morphologic features can be compared. Measurement A is greater in group IV than in group I (pneumatic vs. arrested development). Measurement D is slightly greater in bones with pneumatic than in those with arrested development, as is measurement F. Measurement L differs more markedly between groups I and IV than does any other feature; this difference is in accordance with Wittmaack's views.

TABLE 23.—*Bones of Children Under 16 Years of Age*

Maturation Age	Specimen	Phase of Pneumatization	Maturation Age	Specimen	Phase of Pneumatization
7 fetal mo.	1885 R & L	I	6 mo.	2488 R & L	I
7 fetal mo.	2472 R & L	I	6 mo.	1148 R & L	I
7 fetal mo.	2431 R & L	I	6 mo.	2081 R & L	I
7 fetal mo.	2271 R & L	I	1 yr.	1168 R & L	I
7 fetal mo.	2201 R & L	I	1 yr.	2075 R & L	II
7 fetal mo.	1919 R & L	I	1 yr. 1 mo.	2017 R & L	II
7 fetal mo.	1465 R & L	I	1 yr. 1 mo.	1950 R & L	II
8 fetal mo.	1845 R & L	I	1 yr. 4 mo.	1435 R & L	I
8 fetal mo.	2149 R & L	I	1 yr. 7 mo.	1385 R & L	II
8 fetal mo.	1620 R & L	I	Under 2 yr.	829 R & L	I
8 fetal mo.	2119 R & L	I	2 yr.	2322 R & L	II
8 fetal mo.	1689 R & L	I	2 yr. 7 mo.	1557 R & L	I
8 fetal mo.	2134 R & L	I	3 yr. 11 mo.	1115 R & L	II
9 fetal mo.	2455 R & L	I	4 yr. 8 mo.	2240 R & L	II
9 fetal mo.	2183 R & L	I	5 yr. 5 mo.	2144 R & L	I
9 fetal mo.	1884 R & L	I	5 yr. 8 mo.	1074 R & L	III
9 fetal mo.	2349 R & L	I	6 yr. 1 mo.	624 R & L	III
9 fetal mo.	2436 R & L	I	6 yr. 4 mo.	1784 R & L	I
Less than 1 mo.	2396 R & L	I	6 yr. 6 mo.	1098 R & L	I
Less than 1 mo.	273 R & L	I	6 yr. 9 mo.	632 R & L	III
1 mo.	1462 R & L	I	6 yr. 9 mo.	1156 R & L	II
1 mo.	278 R & L	I	7 yr. 5 mo.	2074 R & L	II
1 mo.	240 R & L	I	8 yr. 11 mo.	1834 R	II
1 mo.	232 R & L	I	8 yr. 11 mo.	1834 L	I
1 mo.	1432 R & L	I	9 yr. 4 mo.	526 R & L	III
2 mo.	2302 R & L	I	9 yr. 6 mo.	2036 R & L	II
2 mo.	1700 R & L	I	9 yr. 8 mo.	872 R & L	III
2½ mo.	293 R & L	I	10 yr. 3 mo.	1688 R & L	I
2½ mo.	2124 R & L	I	10 yr. 6 mo.	404 R & L	III
2½ mo.	230 R & L	I	11 yr. 1 mo.	710 R & L	II
3 mo.	816 R & L	I	11 yr. 10 mo.	1441 R & L	II
4 mo.	818 R & L	I	11 yr. 11 mo.	1772 R & L	II
4 mo.	2247 R & L	I	12 yr. 9 mo.	633 R & L	II
5 mo.	1619 R & L	I	13 yr. 8 mo.	1240 R & L	III
5½ mo.	1453 R & L	I	15 yr.	1041 R & L	III

Total number of bones in each group: I, 93; II, 29; III, 16; IV, 0.

No inference can be made from the angle of the posterior root of the zygoma in predicting the proximity of the lateral sinus to the depression of Wilde (or for practical purposes, to the posterior wall of the external auditory canal). If the reader will refer to tables 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19 and 20, he will notice that there is no constant relation between arrest or nonarrest of pneumatization and the size of the angle. Therefore, the independence of the form of the posterior root of the zygoma from all other bony features must be emphasized.

A bony dehiscence was found to exist between the canal for the carotid artery and the tympanic cavity (anterior part) in specimens 1013 R and 1203 R (series representing ages 55 to 65). A bony dehiscence was found also in the wall between the jugular fossa and the tympanic cavity (inferior part) in specimens 1280 R, 554 R, 554 L (series representing ages 55 to 65), 1312 L and 1361 L (series of 20 to 30 year old Negro men). A dehiscence was found between the jugular fossa and the posterior cranial fossa high up near the internal auditory meatus in specimens 899 R, 912 R, 1872 R, 797 R (series representing ages 55 to 65), 695 R, 548 R, 519 R (series representing ages 16 to 20), 436 R and 618 R (series of 20 to 30 year old white men). It has no real bearing on the foregoing discussion, but it is interesting to note that of 378 temporal bones 2 were found with a dehiscence in the carotid-tympanic wall, 5 with a dehiscence in the jugular-tympanic wall and 9 with a dehiscence between the jugular and the posterior cranial fossa.

Table 23 lists the 138 temporal bones of children under 16 years maturation age. It was from this series that the standard of development based on pneumatization was selected. It is observed that 93 bones appear in group I, 29 in group II, 16 in group III and none in group IV. It is noted also that the third phase is already reached in this series by the skull of a 5 year 8 month old child. It is sure, therefore, that the third phase can be reached by the sixth birthday. Wilson, Gaardsmoe and Anson,[11] working in the department of anatomy of Northwestern University, found (by the method of Born) that pneumatization had extended in full adult degree throughout the apex in a 4½ year old child. They also mentioned that the marrow spaces were separated from the pneumatic spaces by a plate of bone as thick as the inner table of the petrosa (presumably of the same bone). In this study it has not been possible to detect by roentgenographic examination the presence of pneumatic spaces in the apexes of the pyramids of these 138 bones of children of maturation ages 7 fetal months to 16 years.

In these bones of younger persons, in which the cells are small, the pneumatic spaces cannot be distinguished from the medullar spaces (referring to the apexes) for the very reason that the cells are small, but later, when they have become ballooned and larger, the spaces can be differentiated. Therefore the essential feature is the ballooning of the pneumatic cells, which seems to take place characteristically, but not invariably, later in childhood or more particularly in early ado-

11. Wilson, J. G.; Gaardsmoe, J. P., and Anson, B. J.: The Air Cells of the Petrous Portion of the Temporal Bone, J. Laryng. & Otol. **52**:746, 1937.

lescence, and marks the transition from the third to the fourth phase. I have at present no satisfactory explanation of the high percentage of pneumatic bones in the series of adolescents. In the series of bones from children, after the first birthday specimens representing the first phase become suddenly infrequent. Specimens representing the second phase can be found after the first birthday, and the third phase, after the sixth birthday. No example of the fourth phase occurs until after the sixteenth birthday, though it may occur, as Wilson, Gaardsmoe and Anson have shown, as early as the third phase appears in the present series.

CONCLUSIONS

1. The findings recounted in this study support the theory of pneumatization formulated by Wittmaack.[2]

2. If Wittmaack's theory of pneumatization is extended to include the apical or carotid portion of the pyramid, there is a lowering of the frequency of normal pneumatization.

3. The earliest age at which pneumatization could be definitely detected in the carotid portion of the pyramid by roentgenographic study was 16 years, but that pneumatization has already begun in younger childhood is evident from the study by Wilson, Gaardsmoe and Anson.[11]

4. Roentgenographic classification of pneumatization of the temporal bone follows a definite schedule, so that bones may be classified as follows:

Group I: Pneumatization arrested at or before birth.

Group II: Pneumatization arrested at about the 2 year phase.

Group III: Pneumatization arrested only in that the apex or carotid portion is not pneumatic.

Group IV: Pneumatization extending into the petrous apex in addition to the other areas specified in the text.

5. Wittmaack's explanation for arrested pneumatization of the mastoid portion depends on changes in the mucous membrane of the middle ear and its outpocketings occurring in the first and second year of life. The apex or carotid portion of the pyramid is now added to the areas subject to normal pneumatization and the period of outpocketing is extended through childhood to adolescence.

6. The earlier the arrest of pneumatization occurs, the closer will be the lateral sinus to the depression of Wilde (or, for more practical purposes, to the posterior wall of the external auditory canal).

7. In the adult specimens (378), mensural differences depend on features of growth and on the factor of pneumatization. Race seems to make no difference.

8. In general, the most extensively pneumatized bones have greater morphologic measurements; accordingly, their volume is greater.

9. In all, 536 temporal bones have been studied; pneumatization in the apical or carotid portion of the pyramid is first roentgenologically detectable after the age of 16 is reached. Of the 378 bones derived from adults, persons over 16, 52 showed pneumatization in the apex. The several series show pneumatic apexes in percentages which compare favorably with those reported by other authors. Marked differences may occur on the two sides of the same skull, as in the example cited in the text in which the right side belonged to group I and the left to group IV. As a rule, however, such differences were less pronounced, being limited to successive groups, such as I and II, II and III or III and IV.

10. In no bone was there found a pneumatic apex with a complete arrest in the external and mastoid portions of the pyramid. It may be concluded, therefore, that the mucous membrane of the middle ear behaves as a unit.

11. A roentgen technic especially suitable for children up to 5 or 6 years of age is presented in the text. The principle is the following: The pyramid is viewed perpendicularly to its longitudinal axis, and in this early period of life pneumatization extends along the axis of the pyramid. A good view of the cavity of the middle ear also is obtained in this position.

12. The roentgenographic study of 20 temporal bones before and after maceration shows no roentgenographically distinguishable features. It must therefore be admitted that the roentgenogram cannot differentiate marrow cells from pneumatic cells, save that the latter, being ballooned, are differentiable in outline.

13. Various landmarks of common surgical use have been used in this study.

14. Morphologic data on 378 adult temporal bones are recorded in tabular form for reference.

15. Morphologic differences in the temporal bone are due to developmental growth and to pneumatic factors. Once the adult stage is reached, differences in certain areas (e. g. dimension B) are negligible no matter what the stage of pneumatization may be, but in certain areas (dimension L) the stage of pneumatization may cause definite variations.

16. A temporal bone may show any gradation of pneumatization from none at all to complete in any or all parts of the pyramid. Since

the apical or carotid part of the pyramid does not begin to become pneumatized until after the second phase has been reached, the relative frequency of apical pneumatization is already limited by those factors which arrest pneumatization in the other parts of the bone.

17. It is desired to emphasize particularly the significant influence which growth, maturation, time and disease have already had on the temporal bone before it is submitted to the clinician for his judgment and operative measures.

Case Reports

MEDIASTINAL ABSCESS FOLLOWING TONSILLECTOMY

G. Edward Tremble, M.D., and P. Hewitt, M.D., Montreal, Canada

The extreme rarity of mediastinal abscess is considered sufficient reason to report the following case.

In a review of the admissions to the Royal Victoria Hospital for the past fifteen years, only 2 cases of mediastinal abscess were found recorded in the surgical wards. This is the first time the complication followed tonsillectomy and a definite diagnosis was made by means of the roentgen apparatus.

The patient had been carefully examined just prior to admission to the hospital and again on admission. Nothing abnormal was found on either occasion, except that on the morning of the operation the patient complained of a slight cold in the head. This was not deemed severe enough to warrant postponing the operation, as the temperature was normal. The only significant factor in the history was that she occasionally complained of an indefinite pain beneath the sternum and in the lower dorsal region.

The patient was taken to the operating room but, contrary to the usual procedure, avertin with amylene hydrate and gas were administered at the patient's request. There was little bleeding during the operation, and she was returned to her room within half an hour, in good condition.

The patient could not be aroused until 4:30 p. m., and at this time she complained of pain in the back and was irritable and restless. During the night she rested poorly and constantly complained of pain in the lower dorsal region. The temperature rose to 101.2 F. and for the next fourteen days ranged from 100 to 103.2 F., following a septic course. The pulse rate varied from 100 to 130, and the respiratory rate, from 20 to 30.

She was seen on the following day by Dr. S. Lewis, who thought, from the symptoms, that she had a partial collapse of the right lung. This was not borne out by physical findings or by roentgen examination.

During the next five days she complained of pain in the lower dorsal region and under the sternum. She also complained, at times, of pain in the knees, ankles, elbows, shoulders and wrists. On numerous occasions she had "chilly" sensations which were followed by a rise in temperature; she would then perspire freely and the temperature would fall.

During the first five days she had no nausea or vomiting, but on the morning of the sixth day she complained of feeling nauseated, and shortly after this she vomited what at first was thought to be grape juice. This was repeated several times during the day, the vomitus becoming lighter in color each time until finally it was creamy white. On examination under the microscope it was found to be pus. Miscroscopic examination of the pus revealed a mucopurulent material containing

Read before the Montreal Otolaryngological Society, Feb. 10, 1938.

large numbers of polymorphonuclear cells and a wide variety of organisms: many gram-positive cocci in irregular clusters and some gram-positive cocci in chains, many rather large spirochetes and many gram-positive rods, most of which resembled acidophils. Two acid-fast and alcohol-fast rods were found. Cultures revealed the usual organisms of the throat and also pneumococci that were not of type I, type II or type III. These organisms were injected into 2 guinea pigs; 1 died at the end of six weeks, and the other was killed at the end of three months. No evidence of tuberculosis was found in either of the animals at autopsy. The culture showed no growth of tubercle bacilli.

Roentgenogram taken after ingestion of a barium meal. The upper arrow indicates the passage of the barium into the mediastinum. The lower arrow indicates the presence of the barium in the esophagus.

Each day the patient vomited from two to five times, the amount of pus varying from 15 to 150 cc.

Repeated examination of the chest and roentgen examinations revealed nothing. Finally, on the thirteenth day after the operation, the patient was taken to the x-ray room at the suggestion of Dr. Archibald. Barium sulfate was given by mouth and she was examined fluoroscopically. This examination disclosed a fistula extending from 2 inches (5 cm.) below the cricoid cartilage into the mediastinum. The report stated: "The barium sulfate passed slowly through the

esophagus, which was irregularly stained about 2 inches below the cricoid cartilage. From this point an irregular stream passed backward and downward into the mediastinal spaces."

Postural drainage was then instituted, with good results. The temperature became normal on the fifteenth day and remained so. The amount of pus expectorated steadily diminished, and on the thirty-sixth day the patient was taken to the x-ray room again; barium sulfate was given by mouth for fluoroscopic examination. It was found that the mixture no longer entered the mediastinum. During this time the white blood cell count ranged from 10,000 to 14,500. The treatment throughout was conservative. The fluid supply was maintained by intravenous injections and rectal instillations of dextrose. Later, sterile fluids were given by mouth without ill effect.

Three months after the patient's discharge from the hospital she was examined and found to be in normal health.

PHARYNGEAL LYMPHOBLASTOMA SIMULATING RETROPHARYNGEAL ABSCESS

LOUIS BLUMENFELD, M.D., AND MILTON D. GOLDFEIN, M.D., BROOKLYN

While the pathologic entity of pharyngeal lymphoblastoma is not rare and there should not be any unusual difficulty in making a diagnosis in the average case, the symptoms presented by our patient for a time so masked the picture that several diagnoses were discussed. It was not until surgical intervention, with removal of a section for pathologic study, that the diagnosis became evident.

Lymphoblastoma is commonly referred to as lymphosarcoma. However, some authorities like to make a distinction between the two. To quote Delafield and Prudden:[1]

> There may occur in any part of the lymphatic system a tumor composed of lymphocytes (*lymphocytoma*) or, more generally, of their ancestral element, the lymphoblast (*lymphoblastoma*). This type of growth is often called a *lymphosarcoma*, but as there is an increasing desire on the part of pathologists to preserve the term sarcoma for neoplasms of supporting connective tissue, *lymphoblastoma* has been suggested as a substitute.
>
> The parenchyma of an affected node is entirely destroyed, its follicles and lymphcords being no longer recognizable, while the capsule and surrounding tissues are densely infiltrated by tumor cells, elements resembling in size, shape, and appearance the large mononuclear leucocyte.

Along the same line, Ewing[2] said:

> Primary pharyngeal lymphosarcoma is a very common type, and the fact, that with the cervical forms they constitute the majority of the cases, suggests that an infectious agent commonly enters through this area (Chiari, Lit.). The initial symptom is a swelling of lymphoid tissue and diffuse infiltration of mucosa of tonsillar ring or pharyngeal wall, and the early appearances are characteristic (Kundrat). According to Eisenmenger the process regularly begins in the pharyngeal mucosa and not in the tonsils. Yet in several cases at the Memorial Hospital the disease was recognized shortly after removal of enlarged tonsils. . . . Ulceration is soon established, and remains a persistent or recurring complication.

Ewing further stated:[3]

> Lymphosarcoma, representing a lawless proliferation of reticulum cells and their derivatives, may be attributed, *a priori*, to any irritant which influences these unstable cells over a considerable period or in a specific manner. There is no

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From the otolaryngologic service of Dr. E. L. Berger, at the Jewish Hospital.

1. Delafield, F., and Prudden, T. M.: Textbook of Pathology, ed. 16, Baltimore, William Wood & Company, 1936.

2. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 417.

3. Ewing,[2] p. 420.

urgent necessity for assuming the existence of any unknown microörganism or any other occult factors in the origin of this process, for when the above principle is applied in the study of cases a large proportion of lymphosarcomas are reasonably accounted for.

REPORT OF CASE

A 12 year old boy, referred to the office of one of us (M. G.) on June 22, 1936, had been sent home from school with a heavy "cold in the head" two weeks previously. Two days before he was brought to the office, he had begun to complain of pain on swallowing, his speech had become nasal, and a swelling had appeared in the cervical region on the left side.

When seen the child did not appear ill. He had no fever. He was breathing through his mouth and showed definite signs of nasal obstruction.

Examination.—The throat showed a swelling in the left parapharyngeal and retropharyngeal space at the level of the tonsil. The tumor was soft and fluctuant to the touch. The mucous membrane did not seem especially inflamed. There was a postnasal discharge. Both nares were filled with a mucopurulent material, but after suction no definite signs of an acute sinal infection were visible. Transillumination showed the sinuses to be normal. Externally, in the cervical and submaxillary regions there was a hard and somewhat tender mass of glands, which showed no adherence to the skin. The impression obtained at the time was of a retropharyngeal abscess. The soft mass within the throat was incised, but no pus was obtained. As examination of the patient twenty-four hours later showed no change in the pathologic picture, he was advised to go to the hospital for further study.

On June 24 the patient was admitted to the service of Dr. E. L. Berger at the Jewish Hospital in Brooklyn. Dr. Berger reported his examination as follows: "There is a large mass in the cervical region which is tender and hard but not adherent to the underlying skin. The throat reveals a parapharyngeal mass on the left side extending into the epipharynx. There is evidence of a recent incision, through which protrudes some necrotic material."

The temperature, pulse and respiration were normal. The laboratory reported 4,300,000 red blood cells, 11,200 white blood cells, 67 per cent polymorphonuclears and 80 per cent hemoglobin. Cultures of material from the throat were negative. The roentgenograms showed broadening of the retrolaryngeal and retropharyngeal spaces, with straightening of the cervical part of the spine. These conditions suggest a retrolaryngeal and retropharyngeal bulge such as is commonly due to adenitis or abscess.

Course.—A tentative diagnosis of low grade pharyngeal infection and adenitis without suppuration was made and expectant treatment instituted. The mass, both internally and externally, became progressively larger without evidence of any fluctuation. On July 7, fourteen days after admission of the patient to the hospital, we decided, with the thought that we might obtain pus, to incise this mass. On incision, however, no pus was found. That night the patient began to be dyspneic, and at midnight an emergency tracheotomy was necessary. After this procedure he began to show improvement and the external swelling as well as the mass in the throat became smaller. Four days after the operation the patient was so much better that the tracheotomy tube was removed. The next day adhesive tape was placed over the tracheotomy wound in an effort to close

the incision. The patient remained fairly comfortable until July 17, when we were forced to replace the tracheotomy tube because of increasing dyspnea. The mass in the throat again became larger and soon extended past the midline. The cervical mass also increased in size. Throughout this period the patient's general condition was good, his blood was normal and no other glands were enlarged.

On July 21 a section of the pharyngeal growth and two glands were removed for microscopic study. Without waiting for the pathologic report, we instituted roentgen-ray therapy on the assumption that we were probably dealing with a

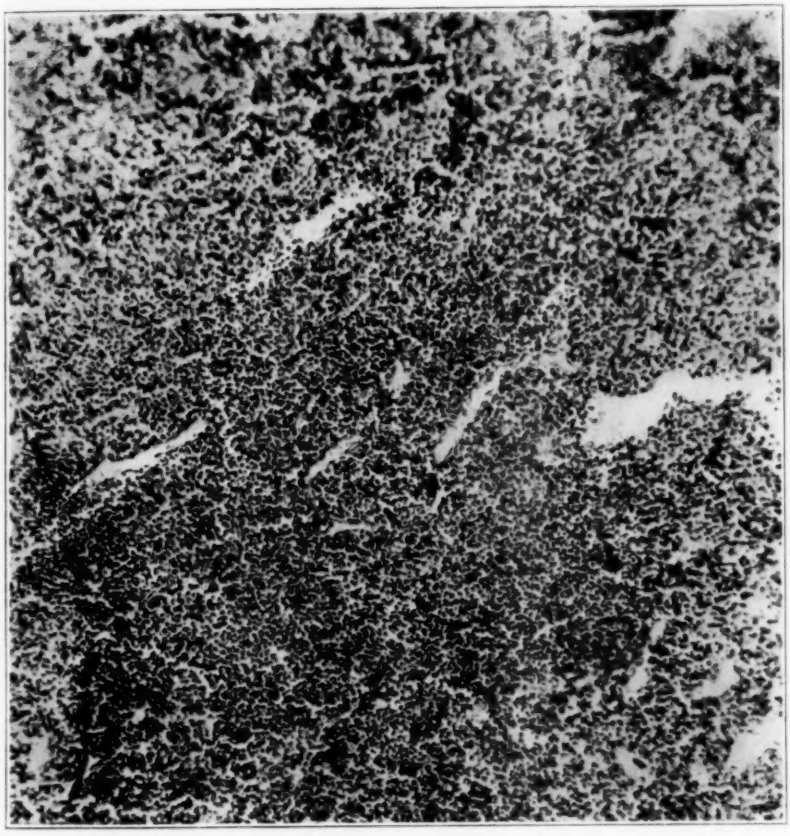

Fig. 1.—Photomicrograph (× 200) of a section of the pharyngeal growth showing the general topography of the tumor.

new growth involving the lymphatic system. Daily studies of the blood showed nothing abnormal.

On July 27 the patient began to bleed from the nasopharynx. The bleeding grew progressively worse in spite of all attempts to control it. After two days he received 350 cc. of blood given by the direct method. The oozing continued. On July 31 the patient was taken to the operating room for ligation of the external carotid artery to control the bleeding. The tumor mass so involved the

carotid sheath and its vessels that it was impossible to expose the artery. He died that night.

Laboratory Report.—Gross examination of the section that had been removed revealed a specimen consisting of two firm portions of tissue, measuring 1 by 0.5 by 0.4 cm. and 1.5 by 1 by 0.7 cm., said to be a lymph node. The external surface was smooth and bore several tags of fibrous tissue. The cut surfaces were composed of gray tissue, in which some red areas were embedded.

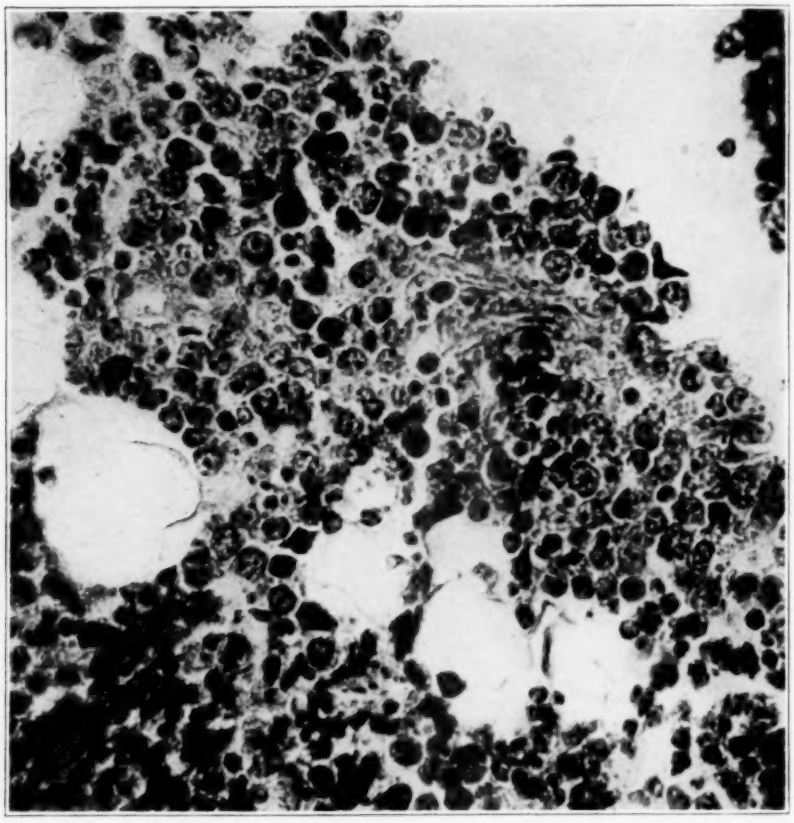

Fig. 2.—Photomicrograph (× 500) of a section of the tumor under high magnification, showing the round cells, with vesicular deep-staining nuclei, scant cytoplasm and indistinct borders.

When a longitudinal section through each portion of tissue was taken for microscopic study, the structure of the lymph node was seen to be distorted by an infiltration of small round cells having large vesicular nuclei and a narrow rim of cytoplasm with indistinct borders (figs. 1 and 2). The sinusoids elsewhere and the subcapsular sinusoids were infiltrated, and the cellular infiltration extended into the nearby adipose tissue, leaving large groups of adipose tissue cells (fig. 3). In the periphery here and there was an infiltration of freshly

extravasated blood and some polymorphonuclear leukocytes, with their nuclear fragments. In another preparation a diffuse infiltration with cells having deep-staining nuclei was more noticeable; the cells appeared in groups and filling sinusoids. A compression of the peripheral cells near the germinal centers was seen. The nuclei of the infiltrating cells appeared to be somewhat larger than the nucleus of a lymphocyte but smaller than that of lymphoblast. In a third preparation the architectural outlines of the lymph node were partly preserved, the distortion being comparatively slight. The germinal centers were active and the sinusoids con-

Fig. 3.—Photomicrograph (× 200) showing the invasion of the adipose tissue by the tumor.

tained deep-staining cells and some red blood cells. The cellular infiltration extended beyond the capsule at some points. Preparations stained by the May-Grünwald method gave no additional information. The nuclei of the infiltrating cells were deep staining. Nuclei in a state of mitotic division were few. The infiltrative character was evident by the passage of the cells beyond the borders of the node and by the infiltration of the nearby adipose tissue.

Diagnosis.—The final diagnosis was lymphoblastoma.

COMMENT

From this case we learned that the usual symptoms referable to the upper part of the respiratory tract may be the forerunner of an unusual underlying pathologic condition. The acute onset, the age of the patient and the symptoms were entirely misleading. We therefore suggest that when a physician is confronted by a definite chain of symptoms indicative of a common disease he should bear in mind the unusual conditions that may cause the same group of symptoms.

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Clinical Notes

AN ACCURATE METHOD OF DESCRIBING THE COLOR OF MUCOUS MEMBRANE

E. R. Hargett, M.D., Springfield, Ohio

At present there is no universally accepted scale in use for the description of the color of mucous membrane, especially of the fine variations that occur in the nasal and turbinate membranes. In fact, most writers are content to picture shades of nasal and of pharyngeal membrane according to their own ideas of the tones of red, or they describe them merely as acid or basic in appearance.

I suggest the general adoption of the Tallqvist hemoglobin scale, with the addition of zero (0) per cent, or intensity, for the description of polyps. The marked change from an intensity of 50 to one of 40 on this scale could well be understood to mark the transition of an acid-appearing membrane, at 50, to one with a basic reaction, at 40.

With such an improved method of determining color, it would be possible for a reader anywhere immediately to note the exact shade the writer had in mind by merely looking at his own easily obtained Tallqvist scale. The method could be used to great advantage also in teaching and lecturing.

First National Bank Building.

A NEW PURE TONE AUDIOMETER FOR SCHOOL USE

Horace Newhart, M.D., Minneapolis

In presenting this new type of audiometer designed for a specific purpose I claim no credit for its technical development beyond the fact that early this year I pointed out to Mr. R. E. Allison, the electroacoustic engineer of a company manufacturing a widely distributed audiometer for diagnostic use, that there exists a large potential demand for a simple, well constructed, pure tone audiometer which could be sold at a low price, especially designed for individually testing the hearing of large groups, particularly school children.

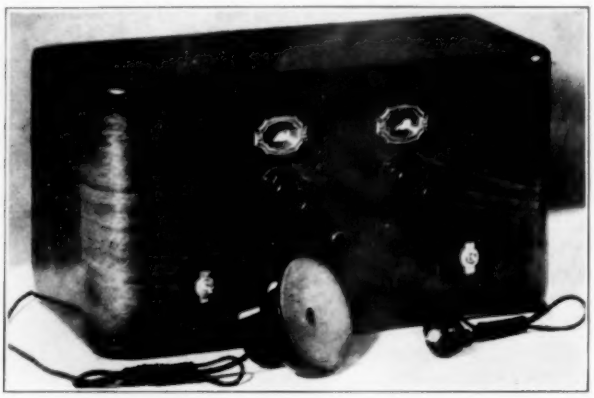
His response was surprisingly prompt. Within three weeks he produced this instrument, known as the maico D-6 school audiometer.

It is a pure tone audiometer with a high grade dynamic receiver. Its operating range is from 128 to 8192 cycles at fixed intervals of one octave with intensities variable in steps of 5 decibels (table).

Presented at the Forty-Fourth Annual Meeting of the American Laryngological, Rhinological and Otological Society, Inc., Atlantic City, N. J., April 29, 1938; at the Seventy-First Annual Meeting of the American Otological Society, Inc., Atlantic City, N. J., May 6, 1938, and before the Section on Laryngology, Otology and Rhinology at the Eighty-Ninth Annual Session of the American Medical Association, San Francisco, June 17, 1938.

It is accurately calibrated and practically meets as nearly as other audiometers submitted the tentative minimum requirements for acceptable audiometers of the Council on Physical Therapy of the American Medical Association, so far as they have been formulated and are applicable to an instrument of this kind.

It has a silent tone interrupter and push button signal light. Outstanding features are the uniform zero reference level and the illuminated, easily read intensity and frequency dials, which together make possible rapid, accurate operation. With it from 30 to 50 persons per hour, or from 150 to 250 per school day,



New maico D-6 school audiometer.

Range of Intensity of the New Pure Tone Audiometer

Test Tone (Cycles per Second)	Range of Intensity (Decibels)
128	70
256	80
512	100
1024	100
2048	100
4096	95
8192	80

can be tested. It is operated by the 110 volt, 60 cycle electric current. Battery-operated models at some additional cost will be obtainable for use in rural schools in which commercial electric current is not available. These features and the low cost ($130.00) make instruments of this type especially desirable for use in public schools and in the student health services of colleges and universities. They will also prove of great usefulness in public health work and in industrial medical practice.

The fact that they do not provide the means for testing by bone conduction and have no masking device precludes their use for diagnostic purposes or prescribing hearing devices. Thus there is avoided the temptation to the nurse or technician to encroach on the field of the practicing physician by making diagnoses.

One audiometer of this type has ample capacity for quickly "screening" a school, college or industrial group containing up to 4,000 or 5,000 persons at a minimum cost. Those found to have deficiency in hearing are rechecked to determine their exact loss of hearing. Although the technic is simple and the tests can be made by a nurse, a technician or a teacher, the work should be done under the supervision of a qualified medical practitioner.

Progress in Otolaryngology

Summaries of the Bibliographic Material Available in the Field of Otolaryngology

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CHRONIC PROGRESSIVE DEAFNESS, INCLUDING OTOSCLEROSIS AND DISEASES OF THE INNER EAR

GEORGE E. SHAMBAUGH JR., M.D.
CHICAGO

The literature for 1937 is unusual for the large number of contributions on nerve deafness. Especially noteworthy are an extensive article, amounting to a monograph, on traumatic nerve deafness by Bunch and a monograph on the pathology of senile deafness by H. von Fieandt and Arno Saxén. The question of the etiology of otosclerosis receives somewhat less attention than usual, but two articles deal with experimental otosclerosis in the fowl with reference to Wittmaack's theory of the etiology of otosclerosis. There are important reports on the results of Gray's intratympanic treatment of otosclerosis with thyroxin as well as several articles on the surgical treatment.

Articles which are merely a repetition of previous work are not included in this summary. My editorial comments are in brackets. The material has been arranged according to the following outline:

Otosclerosis
- Pathology and Etiology
- Treatment

Labyrinthine Deafness
- Pathology of Nerve Deafness
- Hereditary Nerve Deafness
- Traumatic Nerve Deafness
- Nerve Deafness from Drugs
- Nerve Deafness from Infections
- Nerve Deafness from Allergy
- Nerve Deafness from Miscellaneous Causes
- Treatment of Nerve Deafness
- Ménière's Syndrome

OTOSCLEROSIS

Pathology and Etiology.—Nager [1] contributes an interesting discussion of the pathologic changes that occur in the labyrinthine capsule.

1. Nager, F. R.: Disease of the Labyrinthine Capsule: The Pathological Changes, Laryngoscope **47**:161 (March) 1937.

In an attempt to throw light on the etiology of otosclerosis he has studied the effect on the labyrinthine capsule of all known diseases of bone.

The labyrinthine capsule consists of three layers, the endosteal, the endochondral and the periosteal. The endosteal layer is peculiar in that it does not show the constant processes of resorption and apposition seen in living bone elsewhere in the body, whereas the periosteal layer does show these processes. The endochondral layer is characterized by the so-called interglobular spaces, which are remains of its development from cartilage and which persist throughout life.

In senile osteoporosis, when resorption of bone is normal but apposition of new bone is deficient, the periphery (periosteal layer) of the petrous bone looks spongy, whereas the endochondral layer is not affected. The marrow spaces of the periosteal layer are large and filled with a fatty marrow. Rickets and osteomalacia also are observed only in the periosteal layer, the endochondral and endosteal layers of the labyrinthine capsule remaining intact. On the other hand, in osteolysis due to tumors of the eighth nerve or in carcinoma of the middle ear, all layers of bone are destroyed, but the endochondral layer seems to be most resistant.

In suppuration of the middle ear the periosteal layer is easily destroyed, whereas the endochondral layer shows a larger resistance. If inflammatory and necrotic processes start in the inner ear, all layers of bone may be destroyed, but it will be seen that when the inflammation heals the bony tissue does not resemble the old endochondral layer. The newly formed bone shows quite another structure, so that later a differentiation between the cicatricial bone and the primary bone is possible. The hollow spaces of the inner ear are filled with bony tissue, as for instance in deafness after meningitis.

Further evidence of the biologic characteristic of the endochondral layer is shown by the fact that fractures of the labyrinth do not heal, because the endochondral layer cannot produce a bony tissue; consequently fractures through the labyrinth remain open, which is shown by roentgen examination and which, moreover, may be the cause of late meningitis.

In Paget's disease the destruction and new formation of bone start from the periosteal layer. The whole capsule is reformed by unripe bony tissue; the marrow is fibroblastic. In advanced stages even the endochondral layer will be affected in the same way, but generally there remains some small portion of the capsule. It is known that in Paget's disease the stapedovestibular joint may be affected so that the syndrome of ankylosis of the stapes results.

In von Recklinghausen's disease, with tumors of the parathyroid gland, only the periosteal layer is affected in the well known way of formation of fibroblastic bone marrow. This distinctly resembles otosclerotic tissue, and it may be difficult to differentiate the diseases in advanced stages.

In congenital disease of bone the labyrinthine capsule shows typical alterations. In a case of associated athyreosis (absence of the thyroid gland) the endochondral layer was normal but looked a little underdeveloped; ossification of the periosteal layer also was underdeveloped.

In chondrodystrophy, the ossification seems to be normal with the exception of the zones of ossification; they show the same alterations as are known in chondrodystrophy of the extremities.

In osteogenesis imperfecta (fragilitas ossium), the resorption of the cartilaginous tissue is known to be normal, whereas the formation of bone is deficient. This occurs especially in the vestibular part of the labyrinthine capsule, whereas the cochlea remains surrounded by a distinct thin layer of bone.

In endemic cretinism, which is known to be frequent in Alpine regions and which leads to dwarfism and other deformations of bone, the alterations of the petrous bone are so typical that even without knowing anything else about the case the diagnosis of this disease can be made from the ear. There is marked hyperostosis of the promontory, with narrowing of both window niches and certain malformations of the ossicles.

As to otosclerosis, the typical changes show that this disease is to be considered a local osteodystrophy, since the details of the alterations are similar to those in Paget's and von Recklinghausen's disease. The cause of this local osteodystrophy remains unknown.

Cinelli [2] reports the case of a man of 34 with chronic progressive deafness for ten years and a history of fractures 16 different times. His father and paternal grandfather had had many fractures and defective hearing. [Since no bone conduction tests were made, it is not possible to know from the author's report that this was a case of otosclerosis.]

Rainisch [3] tried the effects of epinephrine and pilocarpine in 105 cases of deafness of varying causation. In cases of impaired conduction of sound of the otosclerotic type epinephrine lowered the hearing. This lowering lasted as long as the other symptoms produced by the drug. In early stages of otosclerosis it was marked; in late stages, slight.

2. Cinelli, A. A.: Fragilitas Ossium with Otosclerosis and Blue Sclera: Report of a Case, Arch. Otolaryng. **25**:309 (March) 1937.

3. Rainisch, S. M.: Wirkung von vegetativen Giften auf Schwerhörige, Arch. sovet. otol., 1937, no. 3, p. 64.

In other types of deafness this reaction did not occur. Pilocarpine led to an improvement in hearing in all forms of deafness. This improvement increased gradually up to 50 to 100 per cent toward the end of the first hour and lasted eight to twelve days, the hearing then returning to its former level, with a recurrence of the tinnitus. Repeated injections of pilocarpine led to an increase in hearing of the same duration. Menses somewhat lessened this effect of pilocarpine.

Schkljar and Drennowa [4] occluded the external auditory canal with a hollow tube ending in a capillary tube containing a drop of alcohol, so that movements of the drum membrane resulted in corresponding movements of the droplet of alcohol in the capillary tube. Normally when air is blown into the eustachian tube the outward and inward movements of the drum membrane are equally rapid. The return of the droplet to its initial position can be slowed by various causes. Thus in 86 per cent of patients with otosclerosis the return of the droplet is slowed by a loss of tonus in the drum membrane, probably the result of an insufficiency of the muscles of the middle ear.

Orlova [5] investigated the cholesterol content of the blood in 79 cases of otosclerosis, concluding that the cholesterol is diminished, especially in the early and intermediate stages. During menstruation and with age, there is usually an increase of cholesterol in the blood, so that in elderly patients with advanced otosclerosis an increase of cholesterol in the blood was often found. [Since Russian workers last year reported abnormal amounts of potassium, calcium, nitrogen, chlorides and choline in the blood in otosclerosis, whereas chemical studies of the blood elsewhere have given negative results in otosclerosis, there is some doubt about the value and significance of these Russian reports.]

Schlander [6] states that otosclerosis is rarely observed histologically in the first decade of life and is never seen clinically. Of the cases of otosclerosis in childhood thus far recognized, Manasse has described that of a 3½ year old boy, Weber of a 6 year old girl and of a 6 year old boy, Wittmaack of a 5 year old boy and Scheibe of a 9 year old boy. In each case there was no deafness, the lesion being recognized only on histologic examination.

The author's case is of a 9 year old girl who had had normal hearing except during an attack of acute otitis media on the right side complicated by thrombosis of the lateral sinus and the jugular bulb

4. Schkljar, D. A., and Drennowa, K. A.: Ohrmanometrie bei Otosklerose, Arch. sovet. otol., 1937, no. 3, p. 31.

5. Orlova, E. F.: Otosklerose und Blutcholesterin, Arch. sovet. otol., 1937, no. 3, p. 48.

6. Schlander, E.: Ein Fall von juveniler Otosklerose, Monatschr. f. Ohrenh. **71**:513 (May) 1937.

at the age of 4 years and during occasional attacks of secretory catarrh with head colds. The child died of meningitis following acute otitis media and petrositis of two days' duration. The right ear showed a small focus of otosclerosis at the anterior border of the oval window (site of predilection), and the left ear showed a larger focus in the same region. The footplate had not become involved, and the inner ear on each side was normal.

Altmann [7] sets himself the task of clarifying the question of experimental otosclerosis. He first reviews the previous investigations beginning with a history of the histologic knowledge of otosclerosis. Politzer first accurately described the pathologic picture of otosclerosis and maintained that it was a clinical entity by itself. The finer structure of otosclerotic bone was first studied by Siebenmann, who described (1899) the lacunar areas with osteoclasts and showed that the new bone was demarcated from the old labyrinthine capsule by a sharp, scalloped line, the so-called cement line. Manasse (1912) showed that dark blue-staining, spotted, nonlamellar new bone is first formed in the otosclerotic focus. This new bone is then absorbed by osteoclastic activity and is replaced by lamellar red-staining bone, which finally becomes compact. An explanation of the complicated structure of otosclerotic bone was first offered by O. Mayer (1917), who showed that the original blue-staining bone is repeatedly destroyed by osteoclasts and replaced again by similar bone, until gradually there is formed a maturer red-staining bone, which at first shows only a hint of lamellar structure and later becomes mature lamellar bone. This matured process can flare up and the new lamellar bone may again be replaced by immature blue-staining, spotted bone. By intermingling of these processes the extremely complicated and variable picture of the otosclerotic process occurs. Manasse (1922) then showed that outside the otosclerotic focus changes in the perivascular bone can be seen, consisting of the deposition of new blue-staining bone and called by him "blue mantles."

Concerning the etiology of otosclerosis, O. Mayer and Manasse first pointed out the similarities between otosclerosis and osteitis fibrosa of von Recklinghausen. M. Weber and Nager have also grouped otosclerosis with the reforming diseases of bone, the essential difference being that the otosclerotic process is generally slower, so that osteoclasts are rarely seen.

Wittmaack, unlike the authors mentioned, sought a local rather than a constitutional cause for otosclerosis. By producing (1919) a

7. Altmann, F.: Zur Frage der experimentellen Otosklerose: Nach Untersuchungen an der knöchernen Labyrinthkapsel des Hühnes, Monatschr. f. Ohrenh. **71**:257 (March); 451 (April); 540 (May) 1937.

venous stasis in the region of the labyrinthine capsule in the fowl and reversing the flow of blood, he succeeded in obtaining the same changes in bone that occur in otosclerosis. O. Mayer denied that Wittmaack's findings were experimental and believed that they were due to different ages of the fowls. Kamio (1924) repeated Wittmaack's experiments but obtained no otosclerotic changes. Since then the controversy between Wittmaack and O. Mayer has raged, the views of neither author having received general recognition.

In an attempt to clarify the problem, Altmann proceeds first to study the normal labyrinthine capsule of the fowl in 23 specimens ranging in age from birth to 4 years. He concludes that in the new-born chick a large part of the labyrinthine capsule is already ossified and ossification is complete at about 5 months. As in the human being, the labyrinthine capsule of the fowl has three layers, but unlike the human enchondral layer that of the fowl regenerates bone. Because extensive pneumatization occurs from without and this rebuilding from within, the resulting structure of the labyrinthine capsule is complicated.

To determine the susceptibility of the labyrinthine capsule of the fowl to experimental changes, the author studied 11 more chickens in which osteodystrophia fibrosa had been produced experimentally by the injection of bone marrow pulp. Whereas the rest of the skeleton showed a marked picture of osteitis fibrosa, the changes in the labyrinthine capsule, while similar, were considerably less intense.

Finally, the author examined some of Wittmaack's sections of the petrous bone and concludes that the changes observed by Wittmaack are comparable to the changes observed in human otosclerosis and that they are possibly the result of venous stasis. However, the differences in structure between the human labyrinthine capsule and that of the fowl are so profound that one cannot assume without other evidence that venous stasis plays a role in the production of human otosclerosis.

Oesterle [8] concerns himself also with Wittmaack's experiments on chickens. He first studied 50 temporal bones from normal fowls and concludes that in the human being a solid block of cartilage is replaced by solid bone whereas in the fowl the cartilage is first extensively pneumatized. In the enchondral layer of the fowl bone is actively rebuilt, with a confusion of vessels, while the periosteal layer is composed of parallel lamellas of bone. In the human being, by comparison, the enchondral layer is homogeneous and compact and the periosteal layer is a complicated structure. Of more importance as regards experi-

8. Oesterle, F.: Die normale Histologie und Biologie der Hühnerlabyrinthkapsel im Hinblick auf die experimentelle Hühnerotosklerose, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **143**:362, 1937.

mental otosclerosis than the structure is the biologic nature of the labyrinthine capsule of the fowl. Wittmaack denied that bone is rebuilt after 6 months of age, but the author observes an increase in thickness of the capsule with age due to apposition of bone, while the cartilaginous rests, unlike those in man, decrease in number with age through formation of new bone. In the human capsule, there is no resorption and apposition, so that fractures show little or no tendency to heal and that only from the periosteal layer. The fowl's capsule, however, shows a marked ability to regenerate fairly rapidly by formation of new bone.

In considering experimental otosclerosis in the fowl, one must remember that the normal labyrinthine capsule shows the characteristics of otosclerotic bone, namely, marked filling of the vessels, blue staining of the bone around the vessels and sievelike perforations of this blue-stained bone. Wittmaack later admitted that in 10 per cent of normal fowls spontaneous otosclerosis develops because the pecking and scratching they receive from other fowls results in venous stasis. This, of course, detracts from the validity of any conclusions based on an experimentally induced lesion.

The author then operated on 2 chickens with a third as a control, injecting ferric chloride into the torcular Herophili, and killed one in three weeks and the other in five. In each case thrombosis of the torcular resulted in marked venous dilatation within the skull. Around the thrombus some new bone was formed and where this was close to the labyrinthine capsule the latter showed slightly increased rebuilding of bone. However, these changes were slight and the normal appearance changed only slightly.

The author concludes that the labyrinthine capsule of the fowl differs from that of the human being morphologically and biologically and that the normal capsule shows the criteria for otosclerosis, while producing venous stasis results in no changes in the bone which can be compared to human otosclerosis.

Treatment.—A valuable discussion on intratympanic medication with thyroxin occurred at the combined meeting of the Section of Laryngology and the Section of Otology of the Royal Society of Medicine [9] last year. There were eleven reports of results. A few investigators had obtained improvement in hearing in a small proportion of cases; one reported marked improvement in 11 out of 13 cases, and five considered the results essentially negative.

Two reports are especially noteworthy. Gavin Livingstone, who has continued the treatment begun by Gray in a series of cases and who

9. Discussion on Intratympanic Medication, with Special Reference to Thyroxine, J. Laryng. & Otol. **52**:115 (Feb.) 1937.

therefore should have good results to report if this treatment, which Gray first suggested, has any value, reported on 25 cases in which a total of three hundred and sixty injections were given. No case of infection of the middle ear occurred. In 1 patient violent vertigo developed on injection into one ear and facial paralysis on injection into the opposite; the condition is improving. There were no other complications. Five patients showed improvement measured by the audiometer. Nine ears (in 5 patients) were improved, while 4 ears were worse after the treatment. Subjective improvement in hearing occurred in 8 cases. Tinnitus was improved in 6 of 16 cases.

A series of injections of thyroxin and riboflavin (as a control) into the middle ears of cats failed to show that thyroxin has a specific action causing congestion of the mucous membrane. The author concludes that he is doubtful whether the optimism expressed by Dr. Gray will be fully justified but that further investigation should be carried out.

The other especially important report was by S. C. Suggit, who treated 30 patients with no improvement in 18 and some objective improvement in 12, any improvement, no matter how slight, being included. In the follow-up, however, no sustained improvement in hearing, subjective or objective, has been obtained and in no case has the patient received practical material benefit. In 6 of 22 cases of tinnitus there was complete, or partial relief, permanent so far. In a control series of 11 cases, in which injections of physiologic solution of sodium chloride were used, improvement in hearing could be demonstrated in 7 and in 3 of 6 cases of tinnitus there was improvement. In conclusion, the author states that slight practical results have been obtained by the intratympanic injection of thyroxin and that what results have been obtained were obtained equally well, if not better, by substituting physiologic solution of sodium chloride, which indicates that these results are due entirely to the mechanical effect of fluid in the cavity of the middle ear.

Slightly more encouraging are some of the reports on the surgical treatment of otosclerosis.

Rollin [10] reports the results of operating on otosclerotic patients to arrest the progress of the deafness according to Wittmack's theory, which was discussed in the section entitled "Pathology and Etiology," that otosclerosis is the result of localized venous stasis. This operation, devised by Wittmaack and Methé and called elevation of the dura over the tegmen tympani, is to prevent retrograde venous flow from the plexus around the carotid or the middle meningeal artery into the bone

10. Rollin, H.: Fünf-jährige Erfahrungen mit der Wittmaackschen Otosklerose-operation, Ztschr. f. Hals-, Nasen- u. Ohrenh. **42**:304, 1937.

of the labyrinthine capsule by division of the veins running through the tegmen tympani with the greater superficial petrosal nerve.

The indications for the operation are strict: The diagnosis of otosclerosis must be clearly established from the history, including the absence of earlier suppuration of the middle ear, from the presence of a transparent drum membrane and a patent tube, from hearing tests indicating deafness of the middle ear and from a roentgenogram showing wide pneumatization of the mastoid process. The patient must also recently have become deafer; since the operation hopes only to stop the progress, those whose condition is advanced or stationary are excluded. The operation of Wittmaack is applicable, therefore, only in early, beginning conditions, while the operations of Bárány, Holmgren and Sourdille are for advanced conditions.

Operation has been performed in 60 cases in the past five and a half years. The results in the 45 of these cases in which one year or more has elapsed since operation are as follows: Of the 45, in only 1 did the hearing diminish in the ear operated on, while in 11 the hearing in the opposite ear diminished. There have been no complications threatening to life and no untoward after-effects. The operation is done rapidly and easily by one familiar with the technic. In a small percentage of cases hematoma forms the first day after operation, but it is always absorbed without reaction. In 2 cases in which marked postoperative hematoma occurred, facial paralysis appeared two or three days postoperatively, clearing up in fourteen days and in three months. One patient showed symptoms of labyrinthine irritation, which cleared up without influencing the hearing.

Fowler [11] reviews the rationale of the treatment of otosclerosis. He calls attention to the fact that, while 1 of 20 autopsies on adults shows the presence of otosclerosis, in less than a fourth of these has the disease invaded the annular ligament of the stapes and resulted in clinical symptoms. Up to the present chemical abnormalities of blood have not been found in otosclerosis, so that there is no medical means of combating the condition. Surgically it has not been possible to mobilize an ankylosed stapes.

The author calls attention to the slight variations in hearing with weather, mental states and other factors in otosclerotic patients as in all human beings. These normal variations have been responsible for many treatments for otosclerosis having been given credit for beneficial results. The fact remains that none of them has diminished the otosclerosis or the deafness resulting from it.

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11. Fowler, E. P., Jr.: The Factual Background for the Treatment of Progressive Deafness from Otosclerosis, Laryngoscope **47**:847 (Dec.) 1937.

Recently surgical procedures have been developed which have proved successful in certain selected cases of otosclerosis. These operations aim to create a new mobile window into the labyrinth to take the place of the occluded oval window, so that the normal condition is reestablished, with two movable parts, one to receive sound vibrations and one for the release of sound pressure vibrations.

The author finally calls attention to the fact that one of the chief obstacles to the acceptance of the operative procedures has been the use of hearing tests of doubtful accuracy or completeness, there being doubt as to just how much change is due to the mechanical effects of the operation and how much to the psychologic.

Sourdille [12] reviews the principles underlying his operation for otosclerosis. First, when a permanent window, covered by thin cicatricial membrane, is opened into the perilymphatic space without injuring the membranous labyrinth, the progression of the deafness is completely arrested and the tinnitus diminished or entirely relieved. Second, an opening, no matter how small, suffices, but as soon as it is closed by an osseous callus the progressive loss of hearing resumes. The longest period over which he has observed a case is now seven years.

When the fistula is relatively extensive, 1 mm. wide and 3 to 4 mm. long, and so placed that it receives air-borne sounds directly, one obtains, in addition to an arrest in the progression of the deafness, a definite but slight improvement over the preoperative hearing.

To obtain a really striking improvement it is necessary to carry out a series of transformations of the drum membrane and ossicles, consisting of resection of the head of the malleus and the establishment of a cicatricial plastic flap, called the "internal plastic," which extends from the superior margin of the drum membrane to the labyrinthine fistula and carries sound vibrations across the mobile incus from the pars tensa to the fistula. This operative procedure the author calls the "tympano-labyrinthopexy."

Three operative procedures, separated from each other by several months, are necessary to accomplish this result. The first is the resection of the thick skin from the superior half of the external auditory canal, followed by the formation of a thin, flexible and resistant scar. The second is a complete exenteration of the mastoid cells, with resection of the head of the malleus but preservation of the incus in its normal position, the middle ear cavity being excluded from the operative field by the "internal plastic." The third is the establishment of the laby-

12. Sourdille, M.: Sur le traitement chirurgical de l'otospongiose, Ztschr. f. Hals-, Nasen- u. Ohrenh. **40**:514, 1937; New Technique in the Surgical Treatment of Severe and Progressive Deafness from Otosclerosis, Laryngoscope **47**: 853 (Dec.) 1937.

rinthine fistula and the application to it of the cicatricial membrane. [This procedure is somewhat modified from that described by the author a year ago and abstracted in this review.]

The author has now operated on 140 patients and with this latest technic he obtains positive results for 80 per cent.

Holmgren [13] contributes a paper to the American literature, but since it is only a repetition of the paper published in the *Acta otolaryngologica* the year before and abstracted in this summary last year [14] no further mention will be made of it.

Howarth [15] having personally studied under Holmgren, operated on 7 patients with otosclerosis according to Holmgren's method but met with failure in every case, since the considerable initial improvement in hearing gradually disappeared. He then operated in 1 case, using a modification of his own, as follows: He first did a radical operation but without removing the pars tensa of the drum membrane or the ossicles and then lined the cavity with a Thiersch graft. Six weeks later he elevated the epidermis over the horizontal semicircular canal and removed the bony covering, creating the customary fistula. This method is similar to that of Sourdille except that the operation consists of only two stages. The author states that his operation has been done so recently that the duration of the immediately good result cannot yet be determined.

Hughson [16] reports on 8 cases of "conduction deafness with normal drum membranes" in which operation was based on experiments carried out by himself and Crowe six years before, in which plugging of the niche of the round window was followed by improved electrical response from the eighth nerve of experimental animals. Patients were selected who had a loss of hearing of not more than 50 decibels for the voice frequencies. [The author states that the deafness cannot be of the nerve type, but he does not give any reason for limiting his operation to cases of conduction deafness.] The operation consisted of placing a small piece of fascia removed from behind the ear into the niche of the round window through an incision of the drum membrane after freshening the margins of the window by rubbing gently with cotton. The poorer ear was operated on in each of the 8 cases. [The author reports an improvement in hearing in each case, but careful scrutiny of

13. Holmgren, G.: The Surgery of Otosclerosis, Ann. Otol., Rhin. & Laryng. **46**:3 (March) 1937.

14. Shambaugh, G. E., Jr.: Chronic Progressive Deafness Including Otosclerosis and Diseases of the Inner Ear, Arch. Otolaryng. **26**:583 (Nov.) 1937.

15. Howarth, W.: The Surgical Treatment of Otosclerosis, St. Thomas's Hosp. Rep. **2**:153, 1937.

16. Hughson, W.: Grafts in the Round Window in the Treatment of Certain Types of Deafness, Arch. Otolaryng. **25**:623 (June) 1937.

the published audiograms fails to show a striking or uniform improvement, the variations being similar to the normal variations that are always observed in otosclerosis, with slight improvement at times for certain frequencies but worse hearing for other frequencies, while in some cases the ear not operated on appears to show more improvement than that operated on.]

A contribution by Milstein [17] has some bearing on Hughson's work. Milstein closed the round window in cats with bony fragments, fat, muscle and fascia colli and found that the fascia was best. The animals were then exposed to loud sounds, after which the ear was examined histologically. He noted that the animals operated on showed practically no degeneration of Corti's organ as compared with degeneration of all elements of Corti's organ in the control cats. He concludes that closure of the round window is a protection against the influence of loud sounds on the endings of the eighth nerve [presumably by diminishing the intensity of sound vibrations reaching the cochlea; i. e., closing the round window leads to a diminution in hearing].

Reports on the treatment of otosclerosis by medical or physical therapeutic means were somewhat fewer than usual in the literature for 1937.

Seiferth,[18] having noted the histologic similarity between otosclerosis and osteitis fibrosa of Recklinghausen, has carried out new studies on the mineral metabolism in otosclerosis with the following results: Of 15 otosclerotic patients, 6 showed hypercalcemia and 6 more a slight elevation in the calcium content of the blood (11 and 12 mg. per hundred cubic centimeters), while in 2 the calcium was normal and in 1 slightly lowered. For all 15 the excretion of calcium in the urine was increased. The phosphorus in the blood was diminished in 6, slightly lowered in 4 and normal in 5. These variations correspond to what is found in osteitis fibrosa of Recklinghausen.

Because of the close relation between mineral metabolism and the endocrine system, the author sought a method of measuring the condition of the endocrine glands in otosclerosis. By means of Abderhalden's reactions, with the interferometer method of Hirsch, it is possible to measure this quantitatively. In all cases the parathyroids showed an increased reaction (indicating involution). In all but 1 of the female patients the value for the testes was increased and that for the ovaries normal. In 2 men a so-called paradoxic value for the testes was obtained. The author concludes that otosclerosis is definitely endocrine

17. Milstein, T. N.: Zur Technik des Verschlusses des runden Fensters im Zusammenhang mit den zugehörigen Fragen der Ohrphysiologie, und Pathologie, Arch. sovet. otol., 1937, no. 3, p. 11.

18. Seiferth, L. B.: Zur Aetiologie und Behandlung der Otosklerose, Ztschr. f. Hals-, Nasen- u. Ohrenh. **42**:298, 1937.

in origin, the disturbance lying in the parathyroids and testes, especially in the parathyroids.

In attemping therapy solution of parathyroid was found impractical because of the expense and the need of hospitalization. A 0.5 per cent solution of dihydrotachysterol, a conversion product of ergosterol, while it has no chemical relationship to the parathyroid extract, can completely replace the latter and has been used for tetany due to underfunction of the parathyroids with excellent results.

Up to now 12 otosclerotic patients have been treated with this solution of dihydrotachysterol. Five have shown a definite improvement in one or both ears (as shown by audiometer curves). The dose is 20 drops daily, gradually increasing to 25 to 30 drops a day, with repeated determinations of calcium and phosphorus. Overdosage is to be avoided.

In the discussion that followed this paper, Leiches stated that in several hundred studies of the blood in cases of otosclerosis he had never found increased calcium values and the phosphorus was always normal.

Selfridge [19] obtained detailed dietary histories and detailed chemical determinations on the blood of 5 patients with clinical otosclerosis. Each patient had or had had at some previous time a diet deficient in one or more vitamins, and each patient showed a slight deficiency in one or more of the chemical determinations on the blood. [None of the patients gave clinical evidence of a deficiency in vitamins nor did the author compare his otosclerotic patients with controls with normal hearing. One suspects that most persons would show equal deficiencies in vitamins in their dietary histories and equal abnormalities in the composition of the chemical blood.] The author then administered vitamin concentrates (A, B, C and D) to the 5 otosclerotic patients and obtained slight improvements in hearing. [These improvements, again, were not sufficient to be convincing.]

Sann [20] administered small doses of roentgen rays over the stellate ganglion in patients with tinnitus and deafness who showed disturbances of the sympathetic nervous system. Considerable improvement in hearing resulted at times. Irradiation of the hypophysis had no influence on the hearing.

Landry [21] applied ionization (previously used in the treatment of suppurative otitis media) in cases of deafness in which the drum

19. Selfridge, G.: Chronic Progressive Deafness from a Nutritional Standpoint, Ann. Otol., Rhin. & Laryng. **46**:875 (Sept.) 1937.

20. Sann, R.: Der Einfluss von Röntgenbestrahlungen des Ganglion-stellatum auf Hörstörungen, Hals-, Nasen- u. Ohrenarzt (Teil 1) **28**:241 (July) 1937.

21. Landry, M.: Behandlung der chronischen, nichteitrigen Ohrenentzündungen mittels der Dielektrolyse in Verbindung mit der Hochfrequenz, Ztschr. f. Hals-, Nasen- u. Ohrenh. **40**:673, 1937.

membrane was intact. The author asserts that experiments have shown that the ionization penetrates not only into the middle ear but into the inner ear from the external auditory canal. A solution of iodine ions is used for adhesive otitis, of calcium ions for otosclerosis and of silicon ions for dry otitis. The coincident use of high frequency diathermy is of value and also is of psychologic benefit. The results in cases of chronic adhesive otitis are better than 6 of 10 patients benefited. In cases of chronic catarrhal otitis the results are even better. In most cases of otosclerosis the tinnitus is diminished; the hearing is improved in one third of the cases in which the condition of the labyrinth is good. [While difficult to disprove without repeating the work, this and the previous articles on the medical treatment of otosclerosis are even more difficult to believe.]

Friesner and Druss [22] on the basis of histologic study of suppurative otitis media in the acute and the healed stage suggest that similar changes in the middle ear may be the result of repeated catheterization and inflation, particles of mucus being injected into the middle ear. They further suggest that the progressive loss of hearing that is observed in spite of repeated and prolonged treatment of the eustachian tube may be the result of the treatment, with repeated insults to the mucosa of the middle ear. In the discussion that followed, Page disagreed with the statement of the harmful effects of inflation with the catheter, having found this treatment of the greatest benefit in the treatment of subacute catarrhal conditions of the middle ear. [It appears that Friesner and Druss fail to differentiate clearly between otosclerosis with alterations of the drum membrane and progressive deafness, chronic adhesive deafness with changes in the drum membrane but without progressive deafness and acute secretory catarrh. For the latter, inflation of the eustachian tube by the catheter is the treatment of choice. In chronic adhesive deafness without otosclerosis there is no progress in the defect in conduction in the absence of recurring acute attacks of otitis media, while in otosclerosis with changes in the drum membrane the progressive deafness has nothing to do with the eustachian tube and the cavity of the middle ear.]

LABYRINTHINE DEAFNESS

Pathology of Nerve Deafness.—H. von Fieandt and Saxén [23] contribute a monumental work on the pathology of senile nerve deafness

22. Friesner, I., and Druss, J. G.: Critique of the Present Treatment of Deafness Due to Lesions in the Conduction Mechanism, Arch. Otolaryng. **26**: 259 (Sept.) 1937.

23. Saxén, A.: Pathologie und Klinik der Altersschwerhörigkeit nach Untersuchungen von H. von Fieandt (†) und Arno Saxén: Vorläufige Mitteilung, Acta oto-laryng., 1937, supp. 23, p. 1.

with a correlation between the clinical findings and the histologic picture. The authors point out that while the clinical characteristics of senile deafness have been known for a long time, the pathologic basis for the loss of hearing has been poorly understood. Zwaardemaker first called attention to the lowering of the upper tone limit and the diminished hearing for high tones which begin at a comparatively early age and become more pronounced with advancing years.

In reviewing previous histologic work on senile deafness, the authors note that Sporleder, finding no definite pathologic changes in the labyrinths of 5 elderly patients examined during life, concluded that the lesion in senile deafness lies centrally rather than peripherally. All other authors, however, have placed the lesion in the inner ear or the auditory nerve. Generally all degenerative conditions of the inner ear have been grouped together as chronic progressive labyrinthine deafness, with pathologic changes in four places: the ductus cochlearis, the spiral ganglion, the finer nerve fibers of the cochlea and the trunk of the eighth nerve. Wittmaack has attempted to differentiate histologically various types of chronic progressive labyrinthine deafness as follows:

Genuine neuroepithelial degeneration, a true primary degenerative process, which involves not only the cochlear duct and Corti's organ but also to a similar extent the vestibular portion, the maculas and cristae acusticae.

Atrophic degenerative changes of the nerve trunk.

Peripheral cochlear degeneration, in which a degenerative atrophy of the so-called peripheral cochlear neurons occurs and all the elements which form this peripheral neuron are generally destroyed, the ganglion cells of the spiral ganglion, the nerve fibers in the osseous lamina spiralis and the hair cells of Corti's organ.

This classification of Wittmaack is the one generally accepted in considering the histology of nerve deafness. In considering which type of pathologic change occurs in senile deafness there is, however, a wide diversity of opinion. The authors set out to clarify this question.

The material for this study was found in a home for the aged, the inmates showing deafness being subjected during life to an otologic examination including otoscopic inspection, hearing tests (whisper and tuning forks) and caloric and rotation tests. Material for histologic study was obtained from 44 of those examined, at an interval of a few days to several months, rarely more than a year, after the last hearing test. The distribution by age was as follows: 50 to 60, 1 patient; 60 to 70, 3 patients; 70 to 80, 10 patients; 80 to 90, 16 patients; over 90, 3 patients. The temporal bones were fixed three to twenty hours post mortem. Of the 44 cases studied, aural changes that could not be

ascribed to age were found in 11, 33 remaining in which the deafness could be termed senile.

The 33 cases of senile deafness were grouped according to the histologic pictures as follows: senile atrophy of the cochlear ganglion, 13 cases; angiosclerotic degeneration of the inner ear, 19 cases; central deafness, 1 case.

The histologic observations in these three groups are described in detail.

Senile atrophy of the spiral ganglion includes the spiral ganglion cells and the nerve fibrils and affects the proximal part of the cochlea (basal coil). The organ of Corti is spared, and arteriosclerosis of the blood vessels is not seen. Any changes that occur in the trunk of the cochlear nerve appear to be secondary to that atrophy of the spiral ganglion rather than primary in the nerve. This confirms the work of Crowe, Guild and Polvogt.

Angiosclerotic degeneration of the inner ear results from sclerosis of the local blood vessels, with disturbed nutrition of the epithelial part of the ductus cochlearis, which shows changes. When the secretory epithelium of the stria vascularis is involved, there is, in addition to the degeneration of the organ of Corti, collapse of the cochlear duct. Angiosclerotic degeneration in the labyrinth is not always accompanied by sclerosis of the vessels of the base of the brain or general cerebral arteriosclerosis. It is frequently associated with a genuinely arteriosclerotic contracted kidney.

The two lesions, senile atrophy of the spiral ganglion and angiosclerotic degeneration of the inner ear, occur together but also separately, since atrophy of the spiral ganglion does not occur in every case of angiosclerotic degeneration of the hair cells and often occurs alone, with a normal organ of Corti.

The case of central deafness was that of a woman aged 77 with arteriosclerotic dementia. The right ear was entirely deaf while the left showed some remnants of hearing. Histologically the peripheral hearing apparatus showed a normal organ of Corti, with few changes in the auditory nerve, the ganglion cells of the spiral ganglion being reduced only in the basal coil. Because of the lack of peripheral pathologic change in spite of profound deafness, a central origin was diagnosed, although the exact location could not be determined. There was an unusually diffuse sclerosis of the arteries of the whole body, with thrombosis of the right iliac artery and gangrene of the fingers of the right hand.

In correlating the clinical with the histologic observations, the authors found that the defect in hearing corresponded to the atrophy of the spiral ganglion cells, so that angiosclerotic degeneration when it occurred alone was often accompanied by no noticeable disturbance in hearing.

The hearing may be not only good but entirely normal to all tests, even when Corti's organ is markedly atrophied and the hair cells entirely absent.

The static labyrinth reacted normally in all cases and showed slight changes histologically.

The authors regard senile atrophy of the spiral ganglion as a condition resulting from wear—a process of exhaustion or using-up peculiar to old age. Central lesions are rarely the cause of senile deafness and are to be suspected when there is loss of hearing for the low tones as well as for the high.

The authors suggest that the shortened bone conduction in old age may be due to angiosclerotic changes, with diminished production of endolymph and collapse of the cochlear duct.

Two articles on the interpretation of histologic observations on the cochlea have a bearing on the changes described by von Fieandt and Saxén.

Werner,[24] discussing the artefacts that occur in preparing sections of the inner ear, comes to the following conclusions:

1. For the interpretation of sections it is extremely necessary not only to recognize artificial and autolytic changes but to understand their causes.

2. In the fixing solution substances are dissolved from the tissue partly by changes in hydrogen ion concentration and partly as the result of alcohol. During decalcification they may be further dissolved.

3. By postmortem autolysis substances come from the tissues into the labyrinthine spaces, where they appear as precipitates. Agonal origin of such precipitates is to be rejected.

4. Precipitates of every sort in the labyrinthine spaces can cause additional changes, solution and diffusion into other spaces, deposits on the walls, sedimentation, thickening and shrinking. Thus membranes can become weighted down and held in normal or pathologic positions.

5. Roof and walls of the ampulla are osmotically crushed by the pyroxylin or by rinsing through fixation, in that the acidity determines the loosening of the endosteum or laceration of the perilymphatic fibers.

6. The weighting down of Reissner's membrane is determined not only by the amount of fluid during life in the ductus cochlearis and scala vestibuli but also by the changes in the fixation and decalcification solutions and in the alcohol and pyroxylin. In this way the position of the membrane can change.

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24. Werner, F.: Ueber artifizielle Veränderungen des Innenohres und Ihre Beziehungen zu den pathologischen Vorgängen, Monatschr. f. Ohrenh. **71**:1017 (Sept.) 1937.

7. The condition of Reissner's membrane is no reliable indicator of the hydrostatic pressure of the endolymph in the ductus cochlearis. By a slight ectasia the increased surface is so small that it has no noteworthy resistance to pressure.

8. The volume of the cupola is influenced by the hydrogen ions and the concentration of the fixation solution, by the duration of fixation, decalcification and dehydration and even by the changes in colloidal state of its substance, but not by osmotic pressure.

9. Shrinkage of the cupola is prevented by embedding in pyroxylin, in gelatin or in artificial exudate or by embedding in exudate during life or in necrotic masses.

10. The variable pictures of the tectorial membrane are explained by shrinkage in its three dimensions, shrinkage, shortening and elevation (as a spiral shortening). Marked shrinkage of the membrane held fast to Corti's organ is mechanically explained without assuming a lessening of its fluid content during life.

11. The different conditions of the otoliths depend above all on the condition of their organic coverings which remain after dissolution of the crystals.

12. The artificial (and autolytic) changes are not separated sharply in position or characteristics from pathologic (intravital) changes and are intermingled on the same portion of tissue in different ways.

Lange [25] points out that difficulty in differentiating antemortem from postmortem changes has made it difficult to correlate the histologic picture with the defects in hearing. In order to determine which changes occurred post mortem the author studied the cochleae of 10 patients whose hearing when tested within twelve hours before death was normal. In 4 cases he found changes which are generally accepted as of postmortem origin: loosening of the epithelial cells of the organ of Corti, with escape of protoplasm from these cells but with a thin, tightly stretched Reissner's membrane and a thick tectorial membrane.

In 5 cases he found changes previously described as "genuine neuroepithelial degeneration," with a flattening of the epithelial cells, the tectorial membrane usually lying flattened on them and Reissner's membrane often collapsed and lying on them so that a flattened, almost homogeneous mass is all that remains of Corti's organ. The author discards the assumption that these changes were present before death, with normal hearing, since this would mean that Corti's organ is not necessary for hearing. Since in 1 patient the cochlea was opened before fixation on one side and left unopened on the other and the opened

25. Lange, W.: Hörleistung und pathologisch-anatomischen Befund im Ductus cochlearis, Ztschr. f. Hals-, Nasen- u. Ohrenh. **41**:209, 1937.

side showed only postmortem changes while the unopened side showed "genuine neuroepithelial degeneration," the author suggests that the latter is due to delayed fixation, with postmortem changes.

In conclusion the author points out that there is no clearcut dividing line between intravital changes, postmortem changes and artefacts, so that for the present there is no consistent histologic picture of the organ of Corti in persons with normal hearing shortly before death.

Lurie [26] studied the histologic picture of the ears of animals experimentally deaf from an operation on the cochlea, from long exposure to intense tones or from chemical poisons or congenitally deaf, obtaining an electrical audiogram before death. The only histologic change that corresponded to loss of hearing was degeneration of the hair cells, with loss of nuclei of these cells. Abnormalities of other structures in the cochlea had no apparent relation to defects in hearing. The external hair cells were the first to degenerate. With these gone and the internal hair cells intact, there was partial loss of hearing. With both external and internal hair cells absent there was complete loss of hearing. The audiogram could, in fact, be accurately predicted from the histologic study of the distribution of hair cells (i. e., if the cells were deficient in the basilar turn and present in the apical turns, the audiogram would show a loss of hearing for high tone).

[The observations of Lurie agree with the statement of Lange that normal hearing with loss of hair cells means postmortem changes, not that the organ of Corti is unnecessary for hearing. In the cases of angiosclerotic degeneration of the inner ear with normal hearing described by von Fieandt and Saxén the condition must therefore be regarded as possibly due to postmortem changes.]

Lewy [27] contributes an article on the pathology of nerve deafness. Injuries at birth, with hemorrhages into and around the eighth nerve at the porus acusticus and where the blood vessels enter the modiolus, may result in partial degeneration of the spiral ganglion and deafness.

The progressive deafness of tabes is usually due to gummatous infiltration of the meninges around the eighth nerve, gradually strangling it. Every syphilitic patient with progressive nerve deafness, whether or not diagnosed as tabetic, should have a spinal puncture, and whenever increased cells or protein are found, indicating an active process, immediate treatment is indicated.

The author believes that not only meningococcic meningitis but also measles, scarlet fever, typhoid and influenza may cause deafness by

26. Lurie, M. H.: Pathology of the Organ of Corti, Laryngoscope **47**:418 (June) 1937.

27. Lewy, F. H.: The Pathology of Nerve Deafness, Laryngoscope **47**:409 (June) 1937.

an inflammatory meningeal exudate in the cerebellopontile angle, with destruction of the acoustic nerve, the ventral nucleus and the tuberculum acusticum and with comparative preservation of the vestibular nerve. He suggests that a spinal tap be performed at the first decrease in hearing through infectious diseases, for diagnosis and to drain infectious material out of the cerebellopontile angle.

Nerve deafness from tumors of the cerebollopontile angle is then reviewed. These tumors fall into the following classes:

1. Tumors of the cerebellum give cerebellar and later medullary and cranial nerve signs from pressure, but the hearing remains normal for a long time, any deafness being due to pressure on the eighth nerve.

2. Tumors of the pons present early paralysis of the extremities and ocular muscles, conjugate deviation of the eyes, sensory disturbances and caloric inexcitability but almost no pressure or auditory symptoms. Little or no deafness but ipsilateral vestibular failure strongly suggests an intramedullary lesion.

3. Glaucomatous involvement of the lateral cistern, usually part of generalized cisternal arachnoiditis, does not involve hearing. If there is loss of hearing in such a case, a tumor behind the arachnoiditis should be suspected.

4. Meningiomas of the posterior fossa occur particularly at the transverse sinus, with no auditory symptoms, at the foramen jugulare, with auditory symptoms entirely in the background, and in the porus acusticus internus, where early subjective and objective symptoms of involvement of the eighth nerve are produced.

5. Tumors of the eighth nerve itself are divided into:

(*a*) Medial acustic tumors, the least frequent variety, and the only one permitting complete surgical removal, are those originating from the free intracranial portion of the nerve. Subjective and objective cochlear symptoms are late as compared with increased intracranial pressure and vestibular signs. Cushing emphasizes that these tumors produce first intracranial and then auditory symptoms. When the hearing varies considerably over a short time, the deafness may be due to hydrops of the eighth nerve analogous to a choking of the optic nerve. [This analogy was suggested in an article by H. Brunner abstracted in last year's summary.[14]]

(*b*) Lateral acoustic tumors are those occurring in the distal portion of the nerve within the internal auditory meatus. Deafness is usually complete many years before intracranial symptoms appear. The internal auditory meatus becomes considerably enlarged, and later the tip of the pyramid is destroyed. These tumors cannot be radically removed,

but repeated reduction by partial removal assures a fairly comfortable life. The facial nerve may be involved but is rarely completely paralyzed.

(*c*) Neurofibromas of the von Recklinghausen type are usually multiple and bilateral, with bilateral deafness and loss of vestibular function.

As compared with these extramedullary causes of eighth nerve deafness little is known of nerve deafness from a lesion of the brain stem or the cortex, except that it is apparently unusual.

Wittmaack [28] makes a prediction that in future studies on the pathogenesis of nerve deafness more attention will be paid to the secretion of endolymph and perilymph and the relation of their pressure. Up to now consideration of diseases of the inner ear has practically overlooked the fact that all parts of the inner ear are so surrounded by endolymph and perilymph that the pathology of the inner ear must basically take them into consideration. These fluids have a true circulation, the perilymph being a diffusion from the network of blood vessels, while the endolymph is secreted by highly differentiated epithelial cells. In the ductus cochlearis the main source of endolymph secretion is the epithelium of the stria vascularis, but part of Corti's organ itself also is a source of endolymph. The author believes that as the result of secretion in Corti's organ itself this organ first unfolds, and therefore this endolymph has a somewhat higher pressure than the rest of the endolymph. The exit for the endolymph in Corti's tunnel is probably the small spaces around the nonmedullated nerve fibers. In the sacculus and utriculus the sensory cells themselves secrete, as does the higher epithelium of the adjacent walls. The exit for the endolymph is the saccus endolymphaticus, to whose epithelium the author ascribes the power of resorption. In the perilymphatic space the flow is from the network of vessels in the walls, from which the perilymph comes as a dialysate, out through the aquaeductus cochleae, but there is also resorption from the venous network of the lining walls. The nerve endings of the cochlea with their blood vessels project into these lymph spaces. The tonus of the nerve endings decides their irritability and is influenced by the relation of the pressure of the labyrinthine fluids. These relations of pressure are centrally regulated.

Hereditary Nerve Deafness.—The German law for the prevention of the propagation of hereditary disease is responsible for the continued interest in hereditary deafness in the German literature.

28. Wittmaack, K.: Betrachtungen über die Erkrankungsprozesse des inneren Ohres auf der Gundlage der Tonuslehre, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **141**:25, 1936.

Lange [29] studied the condition of the teeth in children in the Leipzig Institute for the Deaf and Dumb in an attempt to show that anomalies in the teeth might assist in differentiating hereditary from acquired deafness. Anomalies in the teeth were present in 38 per cent of the children with a history of hereditary deafness and in only 12 per cent of those with a history of acquired deafness. However, the number of cases was too small to have any significant statistical value. The author then demonstrated that dental caries was more frequent in the deafened children than in a control group of children with normal hearing. He suggests that the children with acquired deafness had an inherited weakness of the auditory mechanism associated with an inherited weakness of the teeth. [It seems more logical to ascribe the greater frequency of dental caries among the children in the institution for the deaf and dumb to poor diet.]

Muck [30] repeated the experiments of Huber and Korosi, who found the epinephrine probe test of value in differentiating acquired from hereditary deafness. The test was done on 46 children from the Deaf-Mute Institute of Essen. The test was negative for only 7 of the 46, and since all 7 gave a family history of deaf-mutism and there was no doubt that their deafness was hereditary the author concludes that a negative reaction to the epinephrine probe test is definite evidence of hereditary deafness. A positive reaction, on the other hand, is not sufficient evidence of acquired deafness, since positive reactions were met in cases both of acquired and of hereditary deafness. (If a white line appears on the inferior turbinate after it is stroked with a cotton-tipped probe dipped in epinephrine the reaction is considered positive.) Since he previously demonstrated that any injury of the pial vessels (meningitis, meningismus, trauma) will result in a permanently positive reaction to the test, the author suggests that in acquired deafness there is a disturbance of the pial vessels.

Müller [31] tested Langenbeck's rule that bilaterally symmetric defects in hearing, with an intact vestibular apparatus, are evidence of hereditary deafness. Of 15 cases of hereditary deafness, bilaterally symmetric remnants of hearing were present in only 33⅓ per cent, with vestibular abnormalities in 40 per cent. Of 19 cases of acquired deafness, vestibular abnormalities were present in 73 per cent and remnants of hearing in only 1 case, and in that they were asymmetric. The author concludes

29. Lange, J. H.: Zahnuntersuchungen bei Taubstummen, Ztschr. f. Hals-, Nasen- u. Ohrenh. **43**:38, 1937.

30. Muck, O.: Die Beurteilung der Taubstummheit nach dem Gesetz zur Verhütung des erbkranken Nachwuchses unter der Lupe des Adrenalin-Sondenversuches, Ztschr. f. Hals-, Nasen- u. Ohrenh. **41**:408, 1937.

31. Müller, E.: Der Organbefund bei der ererbten Taubheit, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **142**:376 (Oct.) 1937.

that while Langenbeck's rule holds true part of the time it cannot be relied on for purposes of sterilization because there are too many exceptions. The family history is still the essential factor.

Scheideler [32] also tested Langenbeck's rule on a large number of deaf-mute children and found bilaterally symmetric remnants of hearing in 100 per cent of cases of true hereditary deafness with intact vestibular function, while in cases of acquired deafness this combination was never seen. However, while he admits that symmetric remnants of hearing with normal vestibular reactions are evidence of probably hereditary deafness, he states that for final proof a family history of deafness is required.

Langenbeck [33] believes that without a family history hereditary deafness can be affirmed when bilaterally symmetric remnants of hearing are found, since they are found in 4 of 5 cases of hereditary deafness, but are never found in acquired deafness. Since such remnants of hearing can be demonstrated only with large sets of tuning forks or audiometers, the study of all cases in which the hereditary nature of the condition is questionable should be done in the larger otologic clinics.

Schwarz [34] reviews in detail the diagnosis of hereditary deafness. Two forms of hereditary deafness must be differentiated: 1. The recessive or sporadic type. 2. The dominant type (also called the hereditary-degenerative type). In cases of the dominant type other members of the direct family must be investigated, and since this deafness is a dominant characteristic it is usually not difficult to find other deaf persons. However, the mere fact that the father or mother has inner ear deafness does not prove the hereditary nature of the condition, since acquired inner ear deafness is not uncommon.

In sporadic deafness the family history is more difficult to trace, since the direct ancestors and descendants may be normal. Other cases of deafness will be found just as often in the side branches of the family tree as in the direct line of descent. Church, family and town records must all be searched, and the investigation is usually made easier because sporadic deaf-mutism is practically always complete and difficult to conceal as compared with dominantly inherited defective hearing, with which the patient has only a partial loss and often maintains steadfastly that he has normal hearing.

Parents related by blood are regarded as significant evidence in cases of sporadic deaf-mutism, but close relationship alone is not sufficient evidence of hereditary deafness.

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32. Scheideler, J.: Beitrag zur Differentialdiagnose der erworbenen und erblichen Taubheit, Arch. f. Ohren-, Nasen- u. Kohlkopfh. **142**:336, 1937.

33. Langenbeck, B.: Begutachtung erblicher Taubheit, Erbarzt. **4**:65, 1937.

34. Schwarz, M.: Familiennachweis und Organbefund bei der Begründung der erblichen Taubheit, Erbbl f. d. Hals-, Nasen- u. Ohrenarzt, February 1937, no. 1, p. 1; in Hals-, Nasen- u. Ohrenarzt (Teil 1), February 1937.

A mutation cannot be diagnosed except by the descendants.

The author then goes into the findings in the ear. He is of the opinion that further experience is necessary before Langenbeck's symmetric remnants of hearing can be accepted as valid for diagnosis of dominant hereditary defective hearing.

While vestibular reactions are generally assumed to be present in hereditary deafness, they may be disturbed so that the findings in the ear alone are not conclusive in the diagnosis of hereditary deafness.

The development of speech is of some importance, because it never develops in sporadic deaf-mutism without special instruction but does develop normally in dominant hereditary defective hearing (unless the deafness is profound).

The author concludes that present day thought is opposed to placing the findings in the ear in too great prominence, because they are not conclusive and the same findings that occur in hereditary deafness can also occur in acquired deafness. The findings in the ear are only confirmatory evidence, the family history being of primary importance. Hereditary deafness cannot be diagnosed by exclusion, that is, merely because one cannot determine the cause of inner ear deafness.

Takahashi [35] reports a father and 3 children (2 other children died of nasal hemorrhage) with defective hearing combined with sigmatism, the "s" sounds being replaced by "t" sounds. Hearing tests showed a labyrinthine type of deafness, the sigmatism being due apparently to loss of hearing for high tones. Repeated intermarriages between uncles and nieces in the family for four generations was responsible for this hereditary deafness, the author believes.

Traumatic Nerve Deafness.—Bunch [36] reviews the English literature on occupational nerve deafness, pointing out that "blacksmith's deafness" was first mentioned in 1831 by Fosbroke. While numerous studies have been made on occupational deafness with tuning forks, all authors being agreed that the defect is of the nerve type, involving the high tones more than the low tones, little work has been done with the audiometer. In 1928 Fowler noted the frequent occurrence of a marked dip in the audiogram between 1,000 and 5,000 cycles, most often about 3,000 or 4,000, and suggested that acoustic trauma or toxic neuritis was the cause. In 1936 Shambaugh mentioned a dip in the audiogram at 2048 and 4096 seen in cases of occupational nerve deafness.

The author extensively investigates the diagnosis of occupational deafness by the audiogram, including in the study boilermakers (8 cases),

35. Takanhashi, R.: Labyrinthäre Schwerhörigkeit mit Sigmatismus bei einer Familie, die über mehrere Generationen blutverwandtschaftlich war, Oto-rhino-laryng. **10**:7 (Jan.) 1937.

36. Bunch, C. C.: The Diagnosis of Occupational or Traumatic Deafness, Laryngoscope **47**:615 (Sept.) 1937.

patients deafened from exposure to gunfire (7 cases, large guns; 17 cases, small guns), patients deafened by loud noises in the telephone (6 cases), locomotive engineers (3 cases) and a miscellaneous group of patients with occupational or traumatic nerve deafness (10 cases).

In each group the same characteristic curve was seen: the tones below 1024 were relatively near normal, while there was a sharp dip for the higher tones, most marked for 4096. The deeper the dip at this point, the broader it becomes, involving 2048 and eventually 1024 and the higher tones, above 4096.

In 2 cases of deafness from caisson disease there was quite a different curve: an almost uniform loss of hearing for all tones.

Histologic studies have been made in cases of occupational nerve deafness by Bruhl, Habermann and Guild, and the findings are in agreement: an atrophy of the organ of Corti localized to the basilar turn, with a fairly sharp transition from total loss of nervous elements to a normal nerve, the apical turns being normal.

The author concludes that in traumatic or occupational nerve deafness there is a localized injury to the organ of Corti in the basilar turn leading to the following symptoms:

1. The first evidence is an abrupt dip in the audiogram, usually near c-5 (4096). When a dip of this sort is found, acoustic trauma should be suspected and inquired into.

2. With continued trauma this dip deepens and becomes broader, but many times there is a tendency for the hearing to approach normal for the very high tones, 8192 and above. Little loss for the spoken voice will be noted unless the dip includes c-4 (2048).

3. Low tones (512 down) are least often involved, and when they are involved the loss is never as great as for high tones.

4. The greatest loss consistently appears near c-5.

The author points out finally that all ears are not affected equally by the same trauma. Loud noises have a greater traumatic effect when in a closed chamber.

Minkin [37] tested the hearing of 126 coppersmiths, repeating the tests seven months later. He concludes that damage from noise does not occur equally rapidly in all cases, but depends on the constitutional resistance of the individual ear as well as on the type and intensity of the noise. The earliest symptom is a loss for the tones c-4 and c-5, with shortened bone conduction but normal perception of a whisper. When damage from noise is detected early, the hearing can be preserved by changing the occupation.

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37. Minkin, E.: Zur Frage einer früher Diagnostik durch Lärm verursachten Störungen des Gehörorgans, Vestnik otol., 1937, no. 2, p. 166.

Kawata [38] exposed guinea pigs to a loud noise of an intensity of 105 decibels, with the maximum tone of the noise at about 2730 vibrations. He used the ear muscle reflex as an indication of loss of hearing for this tone. The loss of hearing was greatest after exposure for ninety to one hundred and one hundred and seventy to one hundred and ninety days. Histologic study of 1 guinea pig exposed for one month showed complete destruction of Corti's organ localized to the transition between the basal coil and the second turn. However, another guinea pig, whose ear muscle reflex for all tones disappeared after exposure for fifty days, had a normal organ of Corti when examined histologically but a markedly damaged, nearly absent, spiral ganglion in all turns.

Haarmann [39] describes 4 cases of electrical damage to the ear:

1. Tinnitus and dizziness following an electrical discharge in the receiver but with normal hearing and vestibular reactions (possible traumatic neurosis).

2. Moderate inner ear deafness after a stroke of lightning (organic damage).

3. Staggering gait after a five minute contact with a high tension wire followed by eight hours of unconsciousness.

4. Fracture of the left temporal bone after a two second contact with a power circuit, resulting in a fall of 6 feet (1.8 meters) onto the head.

Hallpike [40] describes a case of deaf-mutism of traumatic origin. A man of 59 had been deaf apparently all his life and certainly from the age of 3 years. There was no family history of deafness and no history of injury to the head. Autopsy showed an old partly healed transverse fracture through the right labyrinth, with advanced degeneration of Corti's organ of both ears and formation of new bone in the perilymphatic spaces of both ears. The author concludes that a fracture of the skull in early childhood led to destruction of the right labyrinth, with infection of this labyrinth, low grade meningitis and invasion of the opposite labyrinth through the internal auditory meatus, resulting in complete deafness.

Blegvad [41] defines concussion of the labyrinth as deafness resulting from a strong and sudden sound, with or without a simultaneous increase in air pressure. Fracture of the temporal bone is not included.

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38. Kawata, S.: Experimentelle Studien über die Lärmschädigungen des Gehörorgans, Jap. J. M. Sc., XII, Oto-Rhino-Laryng. **2**:77 (Sept.) 1937.

39. Haarmann, H.: Zur Frage der Ohrschädigung beim elektrischen Unfall, Hals-, Nasen- u. Ohrenarzt (Teil 1) **28**:49 (Feb.) 1937.

40. Hallpike, C. S.: On a Case of Deaf-Mutism of Traumatic Origin, J. Laryng. & Otol. **52**:661 (Oct.) 1937.

41. Blegvad, N. R.: Modern Views on Concussion of the Labyrinth, J. Laryng & Otol. **52**:265 (April) 1937.

Concussion of the labyrinth was seen chiefly during the war, following explosions of shells and usually associated with other bodily injuries, especially when the person was partly buried by the explosion. At first it was believed that this deafness was permanent and the defect was organic. However, the caloric reaction is always retained, and after the war few veterans obtained disablement benefits for this kind of deafness, because most of those who had had it had recovered their hearing partly or completely. It was found that recovery was most rapid in soldiers who remained at the front and was slowest in those who were sent to base hospitals or home. However, these were not cases of malingering, since deafness was accompanied by extensive sensory disturbances, especially around the ear, nor were they cases of true hysteria, since there was no previous history of hysteria. The author applies the term psychogenic deafness to this condition, since the disturbance lies in the cerebral cortex rather than in the labyrinth.

The diagnosis of psychogenic deafness is indicated by the sudden loss of hearing with retained caloric response, after a loud explosive noise, by variation in the hearing tests from day to day, by tests indicating perception deafness though the hearing for low tones may be impaired more than that for high, by hesitation of the patient before repeated words used in testing and finally by the fact that lip reading is learned rapidly but when the ear canals are plugged the patient can no longer read lips, which proves that he has been hearing.

Certain tricks help to detect psychogenic deafness. The patient is asked, in writing, to sing a song after an initial note is struck on the piano. If he begins on this note, he hears.

In treatment, suggestion may be used. Above all, it is important that the economic aspects be settled so that the patient does not profit by permanent deafness.

Nerve Deafness from Drugs.—Taylor [42] reviews the drugs which may cause nerve deafness. Quinine is the most frequent cause of deafness, individual idiosyncrasy to the drug being the most important factor. Salicylates are second in importance. Alcohol, tobacco, arsenic, lead, phosphorus, carbon monoxide, carbon disulfide, mercury, morphine and the aniline dyes are all listed as occasional causes of deafness. Oil of chenopodium causes deafness in a considerable proportion of the cases in which it is used. The author emphasizes that these chemicals, especially quinine, may cause deafness in the fetus when given to the mother during pregnancy. Quinine should not be prescribed for pregnant women when there is a family history of deafness (suggesting a more vulnerable eighth nerve).

42. Taylor, H. M.: Deafness from Drugs and Chemical Poisons, Laryngoscope **47**:692 (Sept.) 1937.

Taylor [43] brings home to the obstetrician the danger of using quinine during pregnancy or labor. He cites 5 cases of deafness in a child with no family history of deafness or syphilis whose mother had received quinine during pregnancy, at which time she had experienced tinnitus and deafness lasting a varying period.

Pellegrini and Nathan [44] review the experimental work on damage to the ear from quinine. In 1881 Kirshner showed extravasation of blood in the cochlea and semicircular canals resulting from experimental poisoning with quinine, but Gradenigo and Wittmaack showed that these hemorrhages were postmortem artefacts. Wittmaack in 1916 showed alterations of the vestibular ganglion and especially of the spiral ganglion from acute, subacute and chronic quinine poisoning. He found changes also in the basal nuclei and the cerebellum. Seiferth (1935) found no histologic changes in the ear and suggested that cerebral intoxication or vasomotor changes might be present. Wittmaack's finding of changes in the spiral ganglion could be confirmed in only a few experimental rats.

The authors carried out experiments with acute quinine poisoning on rats, testing the vestibular apparatus and noting spontaneous nystagmus. They conclude that quinine acts first on the peripheral vestibular apparatus and later on the centers controlling spontaneous movements of the eye and head. They suggest that the symptoms of acute poisoning from quinine are largely peripheral but are partly due also to central changes.

Falbe-Hansen [45] carried out experiments on patients with salicylates and quinine. Of 41 patients given salicylates, 8 showed no aural symptoms, while 33 showed tinnitus and deafness demonstrable by testing. Spontaneous nystagmus occurred in 10 and vertigo was frequent. After a few days the hearing always returned to normal, with no residual deafness. Quinine caused deafness, tinnitus, a feeling of pressure, perspiration and tremor in each of 22 patients. Of these, 8 were dizzy and 7 had spontaneous nystagmus. In several patients the symptoms were typical of Ménière's syndrome. The authors suggest that altered water content in the labyrinth probably accounts for the symptoms.

Covell and Noble [46] in a series of carefully controlled animal experiments determined the effect on the myelin sheath of the auditory nerve

43. Taylor, H. M.: Prenatal Medication and Its Relation to the Fetal Ear, Surg., Gynec. & Obst. **64**:542 (Feb.) 1937.

44. Pellegrini, E., and Nathan, R.: Sul comportamento del sistema acustico-vestibolare nelle intossecazioni acute e croniche da chinino, Ztschr. f. Hals-, Nasen- u. Ohrenh. **41**:510 and 528, 1937.

45. Falbe-Hansen, I.: Klinische und experimentelle Untersuchungen über den Einfluss von Salizyl und Chinin auf das Gehörorgan, Monatschr. f. Ohrenh. **71**: 1055 (Sept.) 1937.

46. Covell, W. P., and Noble, L.: The Significance of Myelin Sheath Degeneration for the Cochlear Nerve, Ann. Otol., Rhin. & Laryng. **46**:895 (Dec.) 1937.

of quinine, salicylates, staphylococcus toxin and deficiencies in various vitamins. In every instance they observed varying degrees of degeneration of the myelin sheath as compared with controls. The authors conclude that the myelin sheath of the auditory nerve is relatively unstable and its degeneration may be produced by a variety of factors. The changes are more pronounced in the basal whorl of the cochlea, and are more marked peripherally than centrally. The authors point out, however, that since cases of clinical deficiency in vitamins in human beings, such as beri-beri, scurvy, pellagra and rickets, are not accompanied by nerve deafness it is unlikely that lesser degrees of deficiency in vitamins are the cause of nerve deafness. The authors do not believe that degeneration of the myelin sheath of the auditory nerve is an adequate criterion for judging the production of nerve deafness.

Nerve Deafness from Infections.—Ciocco [47] compared the audiograms of a large number of syphilitics with those of nonsyphilitic patients of the same age and found the incidence of nerve deafness not greater among those with syphilis and bone conduction not decreased in the syphilitic as compared with the nonsyphilitic patients.

Among syphilitic patients, nerve deafness was twice as common in those with neurosyphilis as in those without neurosyphilis. Defective hearing was as frequent among those who had received adequate treatment for syphilis as among the poorly treated or the untreated. The author concludes that treatment is neither beneficial nor deleterious to the hearing of the majority of syphilitic patients with nerve deafness. An exception occurs when deafness is associated with early meningeal neurosyphilis, when treatment results in a marked improvement in hearing.

Andersen [48] adds a fifth case to the 4 published cases of congenital syphilis of the labyrinth studied histologically. In a young man of 25 bilateral interstitial keratitis developed, with a positive Wassermann reaction. Energetic antisyphilitic treatment was carried out. At the age of 30 the patient awoke one night with marked vertigo, nausea and vomiting and complete deafness in both ears. The hearing improved somewhat in the subsequent days, but the vertigo persisted, and fourteen days after onset he came to the aural clinic. The right drum membrane showed a large, dry perforation, and a history of intermittent discharge since childhood was given. This ear heard nothing. The left drum membrane was thickened, and the left ear heard the conversational

47. Ciocco, A.: Nerve Deafness from Syphilis, Laryngoscope **47**:572 (Aug.) 1937.

48. Andersen, H. C.: Ein Fall von kongenitalem syphilitischen Ohrenleiden mit klinischer und pathologischer Untersuchung, Acta oto-laryng. **25**:37 (Jan.-Feb.) 1937.

voice at the ear, with shortened air and bone conduction. There was no nystagmus from rotation but a strong caloric response from each ear. During six weeks while the patient was in the hospital receiving neoarsphenamine, bismuth and arsenic trioxide the hearing in the left ear improved until a whisper could be perceived at 25 cm. A few months later the patient met an accidental death.

Histologic examination showed old nonspecific healed otitis media on both sides, with thickened drum membranes. The labyrinthine capsule on both sides showed extensive gummatous osteomyelitis and periostitis, with erosion into the lumen of the left vertical canal. The semicircular canals on both sides showed an irregular endosteal proliferation of bone extending into the perilymphatic space. There were no bony changes in the cochlea or vestibule. The membranous labyrinth showed, in addition to marked postmortem changes, a tectorial membrane on the right side rolled up into a structureless mass which had broken off here and there from its natural attachment and was dislocated upward. This appearance corresponds to the hypertonic-hydropic degeneration described by Wittmaack as the result of a hematogenous, tympanic or meningeal toxic effect on the cochlea and produced experimentally by him by injecting guanidine or calcium into the middle ear. In this patient the toxic effect was probably from the inflammation of the labyrinthine capsule.

These changes in the labyrinthine capsule are similar to those reported in the previously observed cases, namely, gummatous osteomyelitis, productive periostitis and gummatous periostitis. These are the changes which occur in other bones in congenital syphilis.

Leichenger and Ableson [49] reported a case of meningococcemia without meningitis in which deafness occurred two days after the start of treatment with antimeningococcus serum given intravenously. A lumbar puncture at the appearance of deafness showed normal spinal fluid, and the drum membranes were normal. The authors believe that the exotoxin of the meningococcus caused a nonsuppurative lesion of the inner ear.

Proetz [51] describes brief diplacusis occurring in his own left ear during mild acute suppurative otitis media. The hearing in the affected ear was depressed about 15 decibels throughout the whole tone range, but beginning at 1024 and increasing in degree to the upper limit of hearing the pitch was raised from one fourth of a tone to four and one-half tones as compared with the normal ear. Twelve days after the onset the

49. Leichenger, H., and Abelson, S. M.: Deafness Associated with Meningococcemia, Arch. Otolaryng. **26**:306 (Sept.) 1937.

50. Footnote deleted on proof.

51. Proetz, A.: Diplacusis Binauralis Dysharmonica, Ann. Otol., Rhin. & Laryng. **46**:119 (March) 1937.

diplacusis began to improve, the highest tones being the last to return to normal, seventy-two hours later. The author explains this temporary diplacusis as due to alterations in the strength, length or mass of the vibrating membrane at the base of the cochlea as the result of a local inflammatory process.

Nerve Deafness from Allergy.—Dean, Agar and Linton [52] find in the literature reports of Ménière's syndrome due to allergy, by Duke (2 cases), Proetz (1 case), Yandell (1 case), Vaughn and Hawke (several cases), Urbach and Wilder (1 case), Malone (2 cases) and Rowe (1 case). The authors have observed 7 cases of aural symptoms due to allergy. In 3 cases the Ménière symptom complex appeared, 1 patient being sensitive to certain foods, 1 having associated asthma (cause not determined) at the time of the attack of dizziness and 1 being allergic to milk, butter and cheese. One patient was unconscious during an attack of Ménière's disease due to allergy to Crisco (hydrogenated cottonseed oil). Two patients had nerve deafness with attacks of vertigo, the hearing improving between attacks. (One was allergic to pollen and 1 sensitive to peas.) One patient had migraine and deafness without vertigo, due to sensitivity to wheat.

The improvement in the hearing of some of these patients, shown by audiograms, when the allergic attack was relieved was remarkable. The authors do not make clear whether they ascribe the defect in hearing to changes in the middle or the inner ear, but they imply the latter, since the drum membranes were usually unchanged.

Nerve Deafness from Miscellaneous Causes.—Fowler [53] found that of 99 patients with Paget's disease, deafness was a major symptom in 41, tinnitus in 10 and vertigo in 23. While a few showed loss of hearing by conduction, the typical deafness of Paget's disease is nerve deafness, usually for high tones, but in some cases extending throughout the tonal scale. This nerve deafness is clearly mechanical, due to compression of the internal auditory meatus by the deformed bone or to invasion of the modiolus and labyrinthine capsule. Recent studies have shown that Paget's disease can be definitely differentiated from most other diseases of bone by the much higher determination of phosphatase in the former. Since radiotherapy will arrest the disease in the long bones long enough to control pain, the author suggests that it be used in early stages of nerve deafness from Paget's disease. One patient so treated had a marked decrease in tinnitus and an improvement in hearing, which, however, was gone three years later.

52. Dean, L. W.; Agar, J. S., and Linton, L. D.: Allergic Diseases of the Ear, Laryngoscope **47**:707 (Oct.) 1937.

53. Fowler, E. P., Jr.: Nerve Deafness from Non-Inflammatory Lesions, Laryngoscope **47**:586 (Aug.) 1937.

Because certain investigators have called otosclerosis localized osteitis deformans, the author obtained determinations of the phosphatase in the serum in a series of 14 otosclerotic patients, with only 1 above normal and this 1 just barely above the normal limit.

The author suggests that the nerve deafness that occurs in otosclerosis besides the defect in conduction is often due simply to the loss of hearing for high tones which is commonly found in older people. In a few cases otosclerotic foci around the internal auditory meatus or in the modiolus may press on the nerve and cause nerve deafness. A careful study of the eighth nerve in cases of otosclerosis has failed to substantiate Gray's finding of trophic changes.

Seaver [54] suggests that a reflex contraction of the tensor tympani and the stapedius muscle as a result of irritation of the fifth nerve from malocclusion of the temporomandibular joint causes tinnitus, vertigo and inner ear deafness. [The article is based apparently on pure speculation, with no case reports to show that this actually occurs.]

Scheideler [55] notes that since 1920, when Monson and Wright first referred to a relation between disturbed hearing and function of the temporomandibular joint, there have been a number of articles on this subject, all noteworthy for their lack of otologic basis. In attempting to evaluate these theories the author concludes that such increased function of the muscles of occlusion as occurs after loss of teeth can produce hypertrophy of the internal pterygoid muscles, which might interfere with the action of the tensor veli palatini muscle and lead to tubal occlusion. However, up to now it has not been proved that this actually does cause deafness. The author rejects the possibility of nerve deafness being the result of disturbed function of the temporomandibular joint.

Crawford,[56] in a wide and extensive experience with patients suffering from malocclusion and overclosure, has yet to observe any case of partial deafness in which correction of the bite improved the hearing, though he has observed several cases of vertigo improved by opening the bite and a few cases of temporary diminution in hearing relieved at once by swallowing or by depressing the mandible.

Treatment of Nerve Deafness.—Selfridge [57] obtained a dietary history deficient in one or more vitamins, particularly in vitamin B, in a series of cases of nerve deafness. In most of the patients a definite

54. Seaver, E. P., Jr.: Temporomandibular Joint Malocclusion and the Inner Ear: A Neuromuscular Explanation, Ann. Otol., Rhin. & Laryng. **46**:140 (March) 1937.

55. Scheideler, J.: Untersuchungen über die Beziehungen einer gestörten Kiefergelenksfunktion auf die Gehörorgane, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **144**:59 (Dec.) 1937.

56. Crawford, W. M.: Malocclusion and Its Relation to Ear and Temporomandibular Disorders, Laryngoscope **47**:532 (Aug.) 1937.

57. Selfridge, G.: Eighth Nerve High Tone Deafness from a Nutritional Standpoint, Ann. Otol., Rhin. & Laryng. **46**:92 (March) 1937.

improvement in hearing followed the administration of vitamin B. The author believes that because Covell, whose article is abstracted in the section on "Nerve Deafness from Drugs," found degeneration of the myelin sheath of the eighth nerve associated with deficiency in vitamin B the principal cause of degeneration of the eighth nerve in man is probably lack of vitamin B in the diet. [However, the author's assumption seems entirely unwarranted, since Covell himself pointed out that in cases of clinical deficiency in vitamin B (i. e., beri-beri) nerve deafness is not one of the symptoms. Moreover, the diets reported seem no more deficient than the diet of the average person with normal hearing.]

Kasabach [58] noted improvement in hearing in 6 of 9 cases in which intensive irradiation for carcinoma of the nasopharynx or near the ear resulted in exposure of the ear to the rays. Of the 6 in which improvement occurred, 5 were cases of tumor of the nasopharynx. Although the author mentions that the improvement in these cases may have been due to relief of occlusion of the eustachian tube, he concludes that "roentgen rays may have a therapeutic value on the auditory system in selected cases." [This entirely unwarranted conclusion has already led to considerable harm in the form of unnecessary and useless irradiation in numerous cases of deafness in the vague hope that the rays will improve the hearing!]

Steinberg [59] offers an explanation for poor results in the correction of nerve deafness with hearing aids. Whereas in conduction deafness there is diminished loudness for all intensities of sound, in nerve deafness the ear hears with normal loudness sounds that are thirty or more decibels above threshold. The result is that, while an electrical aid will amplify all sounds equally for patients with conduction deafness, in nerve deafness, when faint sounds are amplified up to threshold, louder sounds will be heard as uncomfortably loud noises. The hearing is not only distorted but actually painful. To avoid this, selective amplification which amplifies faint sounds more than loud sounds will be necessary to obtain satisfactory hearing in nerve deafness.

Ménière's Syndrome.—Dandy [60] has observed an aberrant artery pressing on the eighth nerve in 8 of 170 operations for Ménière's syndrome. Previous observations having shown that in most cases trigeminal neuralgia is due to arterial contacts with the sensory root of the trigeminal ganglion, the author believes that the two diseases are

58. Kasabach, V. Y.: The Effect of Roentgen Rays upon Hearing, Laryngoscope **47**:545 (Aug) 1937.

59. Steinberg, J. C.: Hearing Aids for Nerve Deafness, Laryngoscope **47**: 603 (Aug.) 1937.

60. Dandy, W. E.: Ménière's Disease, J. A. M. A. **108**:931 (March 20) 1937.

entirely comparable and that Ménière's disease is always due to lesions of the vestibular portion of the auditory nerve. [He does not state what these lesions are when there is no aberrant artery, and he does not explain the fact that in most patients with Ménière's syndrome the attacks stop spontaneously after a few years and are relieved by Furstenberg's diet.]

Brown [61] reports on a series of 12 consecutive patients with Ménière's syndrome treated by Furstenberg's low sodium diet with ammonium chloride medication. In all 12 cases the severe vertigo with vomiting was relieved although a few mild attacks occurred in several of the patients.

Aubry and Ombrédanne [62] divide Ménière's disease into the true form due to neuritis of the eighth nerve and an abnormal form associated with chronic suppurative otitis media, in which in spite of intervention on the ear, vertigo and headache persist. In this form pontocerebellar arachnoiditis is combined with neuritis of the eighth nerve. Tumors of the cerebellopontile angle produce a similar picture.

For both forms the authors use intracranial section of the eighth nerve according to Dandy's technic. The results in 29 cases were as follows:

1. Of 14 cases of true neuritis the vertigo was relieved in 100 per cent by total section of the nerve in 8 and section of the vestibular portion alone in 6.

2. In 14 cases of arachnoiditis, 11 patients were cured; 1 was still dizzy because of complicating cerebellar encephalitis, and 2 died of a flare-up of old, apparently healed, meningitis.

3. There was 1 case of tumor of the cerebellopontile angle.

Of the 11 cases in which the vestibular nerve alone was cut, the hearing was much improved in 2, unchanged in 8 and destroyed in 1.

Mill [63] suggests that Ménière's syndrome may be due to an intracellular edema in the labyrinth resulting from a disturbance in water metabolism, since a salt-free diet has led to good results. In addition to giving the salt-free diet, one must rule out occlusion of the eustachian tube, foci of infection, tumors of the cerebellopontile angle, or other neurologic disturbance (tabes, multiple sclerosis, cerebellar tumor).

If in spite of conservative measures the attacks persist, operation is indicated. The author exposes the horizontal semicircular canal

61. Brown, M. R.: The Medical Treatment of Ménière's Syndrome, J. A. M. A. **108**:1158 (April 3) 1937.

62. Aubry, M., and Ombrédanne, M.: Die Behandlung des otogenen Schwindels durch intrakranielle Durchtrennung des Nervus octavus, Ztschr. f. Hals-, Nasen- u. Ohrenh. **40**:509, 1937.

63. Mill, W. A.: The Operative Treatment of Ménière's Syndrome, St. Thomas's Hosp. Rep. **1**:192, 1936.

through a simple mastoidectomy and opens its lumen with a tiny chisel until a needle can be introduced. One cubic centimeter of absolute alcohol is then injected anteriorly. A simultaneous conjugate deviation of the eyes is observed, not always in the same direction. The wound is closed completely. Postoperatively there are more or less marked vertigo, vomiting and diplopia, lasting as long as one week, with nystagmus toward the good ear. Hearing on the side operated on is completely destroyed. Slight dizziness may last several months, and the tinnitus usually persists. All patients were satisfied with the end results, and none experienced a recurrence of the severe vertigo. Seven cases are described in which operation was performed by this technic.

Rutherford [64] makes a trephine opening behind the knee of the lateral sinus and uses a flat retractor or a "cranioscope" to bring the eighth nerve into view. The cranioscope is similar to a cystoscope. The author operated in 1 case of Ménière's syndrome by this method, relieving the vertigo.

Tillé [65] reports 3 cases of aural and labyrinthine symptoms, with glaucoma. The author suggests that there is a form of hypertension of the labyrinth analogous to glaucoma in the eye. [Except for the association of the two conditions in his cases, he offers no proof for this suggestion.]

Dorochenko [66] notes that the etiology of Ménière's disease is still uncertain. Its frequent association with marked abnormalities of the capillary cutaneous circulation has been noted, and presumably the same capillary changes occur in other tissues, including those of the labyrinth. Recently Speransky has shown that a procaine hydrochloride block of the lumbar part of the sympathetic trunk can diminish certain pathologic processes by a rearrangement of the interrelations of the nerves.

The author has used a procaine hydrochloride block of the lumbar part of the sympathetic trunk in 4 cases of Ménière's disease with uniformly good results although previous treatments had had no success. The technic was as follows: The skin at the angle formed by the twelfth rib and the long dorsal muscle is first infiltrated with 0.25 per cent procaine hydrochloride. A needle 10 to 12 cm. long is then introduced, 0.25 per cent procaine hydrochloride being injected as the needle goes in. After penetrating the muscles and the posterior sheet of the

64. Rutherford, R.: Auditory Nerve Section in Ménière's Disease, Brit. M. J. **1**:660 (March 27) 1937.

65. Tillé, H.: Le syndrome glaucome labyrinthique: Note sur quelques observations de vertiges, hypoacousie et bourdonnements associés au glaucome oculaire, Rev. d'oto-neuro-opht. **15**:577 (Nov.) 1937.

66. Dorochenko, I. T.: Contribution à l'étude des rapports de la maladie de Ménière avec l'état trophique des nerfs: Traitement de la maladie de Ménière par le block à la novocaïne, Acta oto-laryng. **25**:262 (May-June) 1937.

renal fascia, the tip of the needle reaches the interfascial space, which is perceived by the cessation of muscular resistance, and the procaine hydrochloride flows in more easily. The solution reaches the renal and the suprarenal flexus as well as the renal capsule, infiltrating also the part of the sympathetic trunk which lies close by.

Immediately after the first block the attacks of vertigo cease. Normal hearing has returned a week after a second injection. Two cases are cited, in each of which attacks of vertigo occurred two or three times a day, with nausea, vomiting, ataxia, nystagmus and defective hearing in one ear. After the first injection of procaine hydrochloride the attacks ceased. A second injection was given a few days later to prevent further attacks, and in these 2 cases there has not been an attack in more than a year.

Wittmaack [67] found that in experimental labyrinthine disturbance with nystagmus toward the sound ear, when the temporal bones were fixed intravitally or immediately after death, the cupola and macula were voluminously expanded. By applying methylamine to the membrane of the round window, nystagmus toward the diseased ear was produced, and histologically the cupola and macula were shrunken (on the good side as well as that of the diseased ear). When labyrinthine and meningeal pressure are increased the cupola is shrunken, while sudden loss of perilymph after the horizontal canal is opened causes it to swell. Caloric and rotatory stimulation cause similar changes in the volume of the cupola. The author concludes that a nystagmus toward the sound side is evidence of a swelling of the cupola due to increased endolymph pressure, while nystagmus toward the diseased side indicates a shrinkage of the cupola (with decreased endolymph pressure). The author does not believe that deflection of the cupola occurs on rotation or calorization.

DISCUSSION OF THE CONTRIBUTIONS TO KNOWLEDGE OF OTOSCLEROSIS AND NERVE DEAFNESS DURING 1937

When one reviews and sums up the literature on otosclerosis of 1937, one can say that there is nothing particularly new or significant to add to knowledge of the etiology and pathology of otosclerosis. On the other hand, the treatment of otosclerosis is a more rapidly changing and developing field. The medical treatment of otosclerosis continues to give negative results, and this statement apparently includes Gray's intratympanic medication. The surgical treatment of otosclerosis, by Wittmaack's method of arresting the disease and by Holmgren and Sourdille's method of improving the hearing, continues to give promising results in the hands of a few.

67. Wittmaack, K.: Ueber die morphologischen Grundlagen der sogenannten Ausfalls-und Reizerscheinungen des Vorhofbogengangsapparates bei entzündlichen Labyrintherkrankungen, Acta oto-laryng. **25**:109 (March-April) 1937.

In the study of nerve deafness there were several important advances during 1937. The so-called neuroepithelial degeneration of Corti's organ may merely be a postmortem artefact. Senile deafness is due to degeneration of the spiral ganglion beginning in the basal coil. The diagnosis of hereditary deafness still depends on the family history. Two types of hereditary deafness are to be distinguished—the recessive type, usually with profound deafness, occurring sporadically in a family, and the dominant type, with more often a moderate defect in hearing, inherited as a dominant characteristic. Traumatic or occupational nerve deafness is characterized by a dip in the audiogram, most marked for 4096 vibrations. Nerve deafness, with or without Ménière's syndrome, may be due to allergy.

Finally, Wittmaack, the most creative and original writer of the present day on otology, makes two new contributions. He predicts that future advances in the etiology of nerve deafness will center around the labyrinthine fluids. He explains nystagmus from vestibular stimulation as being due to changes in volume of the cupola instead of to deflection of the cupola by currents of endolymph.

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Abstracts from Current Literature

Ear

INCREASED ACOUSTIC SENSITIVITY IN DOGS FOLLOWING ROENTGEN-RADIATION OF THE HYPOPHYSIS. W. J. BROGDEN and E. CULLER, Am. J. Physiol. **119**:13 (May) 1937.

Increased acuity of hearing was produced in dogs by roentgen irradiation of the head. This was shown to be due to the effect on the hypophysis of the lowering of the blood sugar. A diabetic subject and a normal dog showed increased acuity when the blood sugar was lowered with insulin and reduced sensitivity when the blood sugar was raised.

NOURSE, Cleveland. [AM. J. DIS. CHILD.]

CEREBELLAR ABSCESS, WITH DIFFUSED SUPPURATIVE LABYRINTHITIS. A. S. FERNANDO and G. DE OCAMPO, J. Philippine Islands M. A. **17**:13 (Jan.) 1937.

Fernando and de Ocampo report a case of otogenic cerebellar abscess with recovery. The patient was admitted because of symptoms pointing to labyrinthine disturbance. Hearing and caloric tests showed that the labyrinth was completely irresponsive; there were phenomena, however, which could not be explained by this condition alone. The direction of the nystagmus, toward the side of the diseased ear, which was not to be expected in a case of destroyed labyrinth, the continuous headache and insomnia and the mode of falling made the authors suspect the presence of intracranial involvement in addition to the diffuse suppurative labyrinthitis. This belief was strengthened by the presence of slight rigidity of the neck on the day before operation. This prompted lumbar puncture, which showed serous meningitis. The meningitis was of the irritative or protective variety. Suspicions were narrowed to a localized intracranial suppurative process —more specially, an abscess of the temporal lobe or of the cerebellum. Symptoms and signs of involvement of the left temporal lobe were lacking. The presence of cerebellar abscess was then evident, and on the morning of the operation (Newman-Jansen endocranial technic) additional, though vague, localizing symptoms appeared in the form of weakness of the grip of the left hand and adiadokokinesia. When labyrinthitis and cerebellar abscess occur together, symptoms are confusing. The patient was kept in the hospital for almost four months. Maximal drainage and minimal traumatism were assured by cautious insertion of a rubber drain. The pus obtained from the abscess was sterile, probably owing to disintegration of the bacteria by an unfavorable tissue reaction. The route of infection must have been through the labyrinth. Lumbar puncture made three months after operation revealed normal spinal fluid, which showed that the patient had recovered completely from the meningitis.

EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.]

DISCUSSION ON OTITIS MEDIA IN EARLY CHILDHOOD (UNDER FIVE YEARS). J. LE MÉE and others, Proc. Roy. Soc. Med. **30**:1293 (Aug.) 1937.

Otitis media in early childhood is discussed in detail by the following men: Dr. J. M. Le Mée, Mr. T. Ritchie Rodger, Dr. J. H. Ebbs, Mr. Stirk Adams, Dr. C. E. Scott, Dr. R. B. Lumsden, Dr. Douglas Guthrie, Mr. E. Watson-Williams and Dr. McNair Scott. Anatomic points in the production of otic infection, various types of involvement of the ear and of the mastoid, analyses of cases, statistical

reports on the incidence of otitis media and sinusitis, the bacteriologic picture, the association of the disease with gastrointestinal disturbances and with pneumonia, its complications, prophylaxis, detailed reports of cases and the operative indications and technic are taken up. Personal views on many of these matters are expressed by the discussers, and some differences of opinion are noted. The subject is reviewed in an interesting and instructive manner.

CAMPBELL, Philadelphia.

NYSTAGMUS PROVOKED IN THE COMATOSE STATE. I. ALFANDARY, Rev. d'oto-neuro-opht. **15**:161 (March) 1937.

Stimulation of the vestibular apparatus during states of coma has generally been thought to result only in abolition of the quick phase of nystagmus, the eyes being drawn in the direction of the slow component. Alfandary studied the vestibular reactions to caloric stimulation of 11 patients in coma, chiefly of apoplectic origin. The results were: (1) loss of the quick component of nystagmus, (2) disturbance of equilibrium between the two phases, so that the rapid phase occurred only at the beginning or the end of the test or persisted with the eyes in the deviated position and (3) slow deviation of the homolateral eye. A possible explanation of these phenomena is that the rapid phase, being the more recent phylogenetically, disappears first; then follows disappearance of associated movements and, finally, of all movements. These three modalities of the response to caloric stimulation do not represent three phases in the evolution of the comatose state. The only constant sign that accompanies progression of the comatose state is elevation of the threshold of excitation. Clinical and experimental researches indicate that the centers for both the slow and the rapid phase of nystagmus are located in the cerebrum, but in different places.

DENNIS, San Diego, Calif. [ARCH. NEUROL. & PSYCHIAT.]

HYSTERICAL DEAFNESS. G. BUZOIANU, Rev. d'oto-neuro-opht. **15**:175 (March) 1937.

Hysterical deafness, especially the unilateral pure form, is rare. Two types are distinguished: pure hysterical deafness and hysterotraumatic deafness. The deafness may be total or partial and may involve one or both ears. It may be isolated or accompanied with paralysis of other cranial nerves, by hemianesthesia of the skin or mucous membranes or by other disturbances of function. The duration of the disease may be a few days or several years, and recovery may occur spontaneously, as the result of an unexpected suggestion. Cases of unilateral deafness offer great diagnostic difficulties, because the preservation of the cochlear reflexes usually observed in cases of bilateral deafness is of no value if hearing is retained in one ear. A valuable diagnostic sign is the absence of a "false Rinne reaction," which is always present in cases of unilateral deafness of organic origin. The case of a young woman with total unilateral hysterical deafness is reported in detail. The nature of the trouble was recognized by the absence of the false Rinne reaction; immediate recovery was obtained by use of suggestion. In the beginning of the illness none of the hearing tests gave any response; after recovery they were normal. A number of cases of hysterotraumatic deafness occurred during the World War, as a result of the explosion of projectiles. Patients with this type of deafness should be referred to a psychotherapeutist.

DENNIS, San Diego, Calif. [ARCH. NEUROL. & PSYCHIAT.]

EVALUATION OF AUDIOGRAMS. E. WIRTH, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **142**:164, 1936.

Wirth studied the form and the differential diagnostic significance of 235 audiograms. In summarizing his observations he states that a greater impairment of hearing capacity on one side readily leads to errors because of overhearing by

the better functioning ear. For this reason, the audiogram of the more impaired ear is reliable only when closure of the impaired ear produces a different curve. Some of the audiograms are roundish and uniform; others are jagged and irregular. The irregular audiograms with deep indentations occur chiefly in cases of congenital hardness of hearing (sporadic deaf mutism) and of injuries of the cochlea. The audiograms of different patients with hardness of hearing rarely correspond in all details. Nevertheless, the 235 examined audiograms could be classified in eleven groups. Comparison of the audiograms with diagnoses made on the basis of examinations with the speculum and with the tuning forks revealed that some forms of audiogram are, to a certain extent, characteristic for disorders such as otosclerosis or cerebral tumor. However, the same or similar curves are found occasionally in association with disorders of entirely different origin. The fact that severe disturbances in sound conduction frequently cannot be recognized from the audiogram is a disadvantage. Consequently Rinne's test is advisable in addition to the audiogram. Hardness of hearing due to central disturbances shows in the beginning a severe reduction in the sphere of the higher tones and later a more uniform contraction of the auditory field, with great differences in the two sides. Similar curves, often with nystagmus, were found in cases of concussion of the brain. In cases of progressive impairment of the inner ear, there is a slow, concentric reduction of the threshold of hearing. Hereditary hardness of hearing is often but not always characterized by identical audiograms on both sides. In siblings, identical audiograms on both sides may be cited as indicative of the hereditary nature of the defect. The author concludes that if the examiner has sufficient experience with an audiometer, the audiogram permits a fairly correct estimation of hearing capacity. However, he warns against an overestimation of the electroacoustic methods and a neglect of the other methods of examination.

EDITOR'S ABSTRACT.

DIAGNOSIS AND THERAPY OF SECRETORY CATARRH OF MIDDLE EAR, WITH ESPECIAL CONSIDERATION OF PUNCTURE OF TYMPANUM. G. CLAUS, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **142**:186, 1936.

According to Claus, a tympanic exudate is easily recognizable if the tympanic membrane is normal and thus readily permeable by light rays. The upper level of the fluid in the tympanum appears as a dark concave line, which moves as the position of the head changes. This line is missing only in the relatively rare cases in which the entire tympanum is filled with exudate. The second characteristic sign of secretory catarrh is the yellowish color of the tympanum. Contraction of the membrane, which is frequent, the author considers less important in the diagnosis of a tympanic exudate. The recognition of such an exudate becomes considerably more difficult if there are pathologic changes on the tympanic membrane. In cases in which the tympanic membrane is thickened a normally invisible level of exudate often becomes visible after air has been introduced into the middle ear. In cases in which pathologic changes in the tympanic membrane makes the recognition of an exudate impossible, thorough anamnesis is important. On moving the head forward and backward, patients with this condition often have a feeling of fluid in the ear. Intelligent persons often state this spontaneously and occasionally report that with the head in a certain position the hearing capacity improves. Some complain of a feeling of pressure or of fulness in the ear. These symptoms indicate a tympanic exudate, especially if the patient has had a cold previous to the appearance of the aural symptoms. The author shows further that, since many patients reject paracentesis if they are free from pain, puncture of the tympanum is helpful not only diagnostically but therapeutically. He performs this puncture with a syringe with 1 cc. capacity and a cannula 62 mm. long and 0.6 mm. in diameter. The puncture is made, if possible, in the anterior lower quadrant, otherwise in the posterior lower quadrant. In five years the

author resorted to puncture of the tympanum in 60 cases of tympanic exudate. The quantities of exudate varied between 5 and 44 cubic millimeters, in most cases between 20 and 30 cubic millimeters. The puncture was followed by inflation of the middle ear with air. In some cases puncture had to be repeated. Complete cure was effected in 53 cases; in the remaining 7, considerable improvement was obtained. The author does not resort to puncture at once but first performs the necessary therapeutic measures on the nose and the pharynx, applies heat to the ear and catheterizes the tubes or resorts to politzerization. If these measures do not produce the desired result, puncture of the tympanum is resorted to.

EDITOR'S ABSTRACT.

PATHOLOGIC AND CLINICAL ASPECTS OF ACUTE MASTOIDITIS. F. ALTMANN, Monatschr. f. Ohrenh. **70**:1465 (Dec.) 1936.

It is Altmann's opinion that among the numerous factors which influence the course of acute otitis or of the resulting mastoiditis, two are of especial significance, namely, the type of the pathogenic micro-organism and the anatomic structure of the mastoid. To be sure, such factors as the age and the sex of the patient may likewise be of influence. The author studied these various factors in 1,457 cases, in 98 of which both ears were operated on. An analysis of the cases according to the pathogenic organisms disclosed hemolytic streptococci in 66.2 per cent, Bacillus mucosus in 18.7 per cent, pneumococci in 10.9 per cent and various other organisms in 4.2 per cent. The paper is accompanied with tables which record the incidence of the different micro-organisms in the two sexes and in the different age groups. These tables indicate that hemolytic streptococci are relatively more frequent in nurslings and particularly in children and young persons than they are in older persons, whereas pneumococci are comparatively rare in young persons but become more frequent later. In discussing the incidence of the various micro-organisms in the two sexes, the author says that pneumococci show a slight predominance in male subjects. Further, he shows that the pneumatization of the mastoid process exerts an influence on the development and the course of mastoiditis. He differentiates four types of pneumatization, one normal and three inhibited types. In the more than half of the cases the mastoid processes showed good pneumatization, but since the course of acute otitis, and with it the tendency toward the development of mastoiditis, is greatly dependent on the anatomic structure of the mastoid process, the incidence of the various types of pneumatization in patients with mastoiditis permitted no conclusion regarding the frequency of the various types in normal persons. The author analyzes the material in regard to the number of days elapsing between the onset of the otitis and the surgical attention, to the relation between this time factor and the age and the sex of the patient, as well as to that between time and the type of infecting organism. The incidence of complications is analyzed with regard to these different factors. The author stresses the high mortality and particularly the high incidence of meningitis in pneumococcic infections.

EDITOR'S ABSTRACT.

CLINICAL ASPECTS OF EXTERNAL PERFORATION IN ACUTE OTITIS MEDIA. K. LÖWY, Monatschr. f. Ohrenh. **70**:1493 (Dec.) 1936.

Löwy points out that suppurations within the mastoid process may, in the absence of spontaneous cure or of surgical evacuation, perforate at various sites. If perforation takes place toward the internal cortex, an extradural or an intracranial complication is the result. If the perforation takes place through the external cortex, however, a periosteal abscess and later a gravitation abscess may result. The author analyzes the perforations in cases of acute otitis or mastoiditis observed at the Vienna clinic between 1927 and 1933. In all cases (2,089 in all), antrotomy was done. The number of cases of periosteal abscess in which the site

of perforation was detected was 475, and there were 101 cases of periosteal abscess in which the site of perforation could not be found. A complicated gravitation abscess was observed only once, a rarity probably due to the fact that generally surgical intervention is made before this complication can develop. The author mentions the various sites at which perforation may take place and then indicates in tables the distribution of the various perforations according to age. He discusses the relation of perforation to pneumatization, to type of pathogenic microorganism and to intracranial complications and the duration of otitis previous to perforation. Intracranial complications are relatively rare in cases of periosteal abscess. The relatively frequent perforation of the internal cortex in cases in which external perforation has already taken place seems to corroborate the opinion of Krainz that there is no relation between perforation and the relief of pressure.

EDITOR'S ABSTRACT.

RELATION OF PNEUMATIZATION TO COURSE OF ACUTE OTITIS MEDIA. H. BARTH, Ztschr. f. Hals-, Nasen- u. Ohrenh. **41**:137, 1936.

This report by Barth is based on 717 cases of acute otitis media which were observed in his clinic in four years. Surgical treatment was resorted to in 510 of the cases, and conservative treatment was employed in the others. There were 20 (2.78 per cent) fatalities from otogenic complications. The author discusses the value of the roentgenogram, pointing out that it gives a good survey over the pneumatization. To be sure, in cases of acute otitis media it is often difficult to estimate the cellular structure (regular or irregular arrangement of cells). The author adopts Schwarz's classification of five different types of pneumatization. Acute otitis media may occur in association with all types, but it is most frequent when there is a good development of the cells. In cases of considerable inhibition of the pneumatization, acute otitis media often heals spontaneously, and surgical treatment is less often needed than when pneumatization is good. The duration of the process is usually greater in cases of spontaneous cure and inhibited pneumatization than in cases of good pneumatization. In patients with unilateral otitis media in whom the pneumatization was different on the two sides, the ear with the poorer pneumatization was somewhat more often diseased than the ear with the better developed cells. Among 13 patients with bilateral otitis media but varying pneumatization, there were 10 in whom the course was the same on both sides; in 3 cases antrotomy had to be done on the better pneumatized ear, whereas the other ear healed spontaneously. Subperiosteal abscesses were observed in all types of pneumatization, but not in ears without pneumatization. Contrary to expectations, subperiosteal abscesses were somewhat more frequent in children between the ages of 5 and 9 years than in those between 2 and 4 years. In the higher age groups subperiosteal abscess becomes somewhat less frequent. The better the pneumatization, the more frequent is the subperiosteal abscess. No relation between the sinal involvement and the degree of pneumatization could be detected except that when there was no pneumatization the sinus was relatively often involved. However, on account of the small number of cases, no general conclusions can be drawn. Complications like labyrinthitis, extradural abscess and nonlabyrinthogenic meningitis were observed chiefly in patients with good or normal pneumatization. In a surprisingly large number of cases influenzal otitis or infection with pneumococci or with Bacillus mucosus affected patients with normal pneumatization. Moreover, in the cases in which there was a fatal outcome, normal pneumatization predominated. However, although there are indications of relations between the anatomic structure of the mastoid process and the course of acute otitis media, there are so many deviations from this rule that in the individual case the prognosis cannot be based on the pneumatization.

EDITOR'S ABSTRACT.

DIRECTION OF NYSTAGMUS IN PRESENCE OF SYMPTOMS OF LABYRINTHINE FISTULA. T. HASEGAWA and M. OKAWACHI, Ztschr. f. Hals-, Nasen- u. Ohrenh. **41**: 168, 1936.

Hasegawa and Okawachi tried to find answers to the following questions: 1. Does the surgical production of a fistula on the semicircular canals produce two types of nystagmus in opposite directions? 2. Can the difference in the two types of nystagmus be explained by corresponding anatomic differences? 3. How can these manifestations be explained? The authors made their experiments on chickens weighing about 2 Kg. It was found that if the fistula was produced in the lateral semicircular canal the nystagmus was horizontal, whereas if the fistula was in one of the vertical semicircular canals the nystagmus was oblique and slightly rotatory (between anteroinferior and posterosuperior). When the rapid phase was directed backward, that is, from anteroinferior to posterosuperior, this was designated as a nystagmus toward the treated side. However, when the rapid phase was from posterosuperior to anteroinferior, the nystagmus was designated as being of the opposite direction. A tabular report indicates that in 5 cases nystagmus was toward the treated side and in 9 cases toward the opposite side. The first question is thus answered in the affirmative. The answer to the second question was furnished by microscopic studies. In the cases of nystagmus toward the opposite side the fistula always was at the site where the wall of the membranous semicircular canal is normally attached to the bone. In cases of nystagmus toward the treated side the fistula was on the wall of the perilymphatic space. These observations seem to indicate that direct pressure on the endolymphatic space produces nystagmus toward the opposite side and indirect pressure on the endolymphatic space produces nystagmus toward the treated side. The reply to the third question is not so simple, for although differences were observed in the size of the cupula and of the subcupular space in the two types of nystagmus, these differences do not provide an adequate explanation.

EDITOR'S ABSTRACT.

Pharynx

RECURRENCE IN MIXED TUMORS OF THE SOFT PALATE. JONATHAN E. RHOADS and PAUL M. MECRAY, Am. J. M. Sc. **193**:389 (March) 1937.

Although mixed tumors of the soft palate resemble those of the parotid gland, recurrence after excision is rare. The authors report an instance of recurrence of such a tumor at the original site eleven years after its removal. Only 2 similar recurrences have been described among 60 cases of mixed tumor of the soft palate recorded in the literature.

LYNCH, St. Paul. [ARCH. DERMAT. & SYPH.]

BASAL-CELLED CARCINOMA OF THE PALATE. W. A. MILL, Proc. Roy. Soc. Med. **30**:922 (May) 1937.

A case of adenocystic basal cell carcinoma of the hard palate is reported. The condition was treated first with radium, and later the tumor and hard palate were excised and the walls treated by diathermy. The result of the treatment is not mentioned.

CAMPBELL, Philadelphia.

TREATMENT OF PERITONSILLAR ABSCESS BY TONSILLECTOMY. ANTONIO E. CARRASCOSA and FERNANDO J. CASTELLANOS, Rev. méd. latino-am. **22**:179 (Nov.) 1936.

The authors advise immediate tonsillectomy in cases of peritonsillar abscess. They contend that the cause is eradicated before the condition becomes toxic and at a time when the patient does not object to the operation. In a series of 200 cases there have been no significant complications.

DWYER, Kansas City, Mo. [AM. J. DIS. CHILD.]

PHLEGMON OF FLOOR OF MOUTH FOLLOWING FOLLICULAR TONSILLITIS. H. BRUNNER, Monatschr. f. Ohrenh. **70**:1436 (Dec.) 1936.

Brunner describes the clinical history of a man aged 45 in whom after follicular tonsillitis a necrotizing suppurating phlegmon developed. It spread from the parapharyngeal space of the left side over the floor of the mouth in the form of a horseshoe. It was found that the phlegmon spread from one side to the other by way of the connective tissue space between the geniohyoid and the genioglossus muscle. From the clinical point of view, this case belongs with those in which the phlegmon takes an extremely rapid course. EDITOR'S ABSTRACT.

SIGNIFICANCE OF TONSILLECTOMY AND ADENOIDECTOMY IN DIPHTHERIA CARRIERS. V. HLAVÁČEK, Časop. lék. česk. **74**:934 (Aug. 30) 1935.

Of 8 children ranging from 8 to 15 years of age who were designated as chronic diphtheria carriers (none had clinical diphtheria), 6 had frequent sore throats and 2 not even this symptom; 4 had congenital syphilis; 7 had enlarged tonsils and adenoids, and 1, merely enlarged adenoids. Cultures were obtained from 4 on the third day after uneventful tonsillectomy and adenoidectomy; the cultures from 3 of these were negative; on the ninth day the cultures from 7 were negative. In 1 case cultures made from the removed tonsils were negative. In another case the culture from one tonsil was negative. The cultures from the adenoids were negative in 4 of the 8 cases. Histologic studies were made of the removed tonsils and adenoids. Tonsillectomy removes cryptic foci in retrotonsillar folds, which are difficult to disinfect locally, and is recommended even for nonchronic carriers from the standpoint of reinfection of cryptic tonsils.

STULIK, Chicago. [AM. J. DIS. CHILD.]

Nose

PARANASAL SINUSITIS. SIDNEY SAMUEL DUSHAN, Arch. Pediat. **54**:643 (Nov.) 1937.

Sinusitis may be classified as extrinsic, intrinsic or of physical or chemical origin. Either of the first two types may be acute or chronic. The extrinsic type is due to foods or excitants; the intrinsic, to bacterial infection. The last type is due either to heat and cold or to chemicals, and instances of it make up only a small proportion of cases of sinal disease.

ORR, Buffalo. [AM. J. DIS. CHILD.]

UNILATERAL CHOANAL ATRESIA IN A WOMAN, AGED 23. T. B. JOBSON, Proc. Roy. Soc. Med. **30**:917 (May) 1937.

Jobson reports a case in which one nostril was obstructed by a complete closure of the choanal opening by a bony wall. No treatment is suggested, but in the discussion similar cases are mentioned and methods of removing the obstruction discussed.

CAMPBELL, Philadelphia.

DISCUSSION ON ORBITAL CELLULITIS DUE TO SINUS INFECTION, AND ITS TREATMENT. E. D. D. DAVIS and others, Proc. Roy. Soc. Med. **30**:1397 (Sept.) 1937.

E. D. D. Davis discusses this subject from the symptomatologic, the diagnostic and the therapeutic standpoint. He mentions 54 cases of edema or swelling of the orbital tissues, in 72 per cent of which the condition was due to suppuration of the frontal or the ethmoidal sinus. He expresses the belief that if an orbital

abscess is present it should be drained promptly but that radical operation seldom is necessary. In many cases cellulitis in children subsides under conservative treatment.

S. H. Mygind bases his discussion on 86 cases of acute swelling of the orbit. He gives statistics covering various phases of his study of these cases, speaks of the frequent difficulty of diagnosis of orbital cellulitis of sinal origin and its dangerous complications and emphasizes the need for thorough operative methods of treatment.

G. H. Howells emphasizes the operative care of patients with orbital cellulitis.

F. C. W. Capps reports a series of cases, with details of the treatment in each case. He expresses the belief that suppuration is a definite indication for the external operation.

E. Watson-Williams distinguishes between the type of orbital involvement in which there is infection between the bony wall of the orbit and the periosteum and the type in which actual infection of the orbital tissues occurs with cellulitis of these tissues and probably abscess formation.

W. Stewart expresses the belief that cases in which streptococci are present operation should be barred in favor of medication with sulfanilamide or serum.

W. S. Thacker Neville advocates the administration of large doses of sulfanilamide.

CAMPBELL, Philadelphia.

NASAL SUPPURATION IN INFANCY: BIOLOGIC TREATMENT. FRANCISCO BLOTTA, Rev. méd. latino-am. **22**:1240 (Aug.) 1937.

Suppurative rhinitis and sinusitis from a variety of causes are described, with the various methods of treatment in common use. The author stresses the value of vaccines and, when the results of bacteriologic studies indicate it, of specific serums in cases of diphtheritic and streptococcic infection. Antistreptococcic serum is used locally in cases of nasal infection following scarlet fever. When vaccines are not effective, operative procedures are considered.

DWYER, Kansas City, Mo. [AM. J. DIS. CHILD.]

Miscellaneous

USE OF PARA-AMINO-BENZENE-SULPHONAMIDE OR ITS DERIVATIVES IN TREATMENT OF BETA HAEMOLYTIC STREPTOCOCCAL MENINGITIS. FRANCIS F. SCHWENTKER, FREEMAN P. CLASON, WILLIAM A. MORGAN, JANVIER W. LINDSAY and PERRIN H. LONG, Bull. Johns Hopkins Hosp. **60**:297 (April) 1937.

Four cases of meningitis due to the beta hemolytic streptococcus are reported. Three of the 4 patients recovered. All were treated with sulfanilamide (para-aminobenzenesulfonamide) or its derivatives.

The authors believe that surgical procedures to eradicate septic foci are indicated in the treatment of streptococcic meningitis as an adjunct to specific therapy but that extensive surgical intervention should not be resorted to until the infection has been brought under control by the specific therapy.

LYTTLE, New York. [AM. J. DIS. CHILD.]

LACK OF FITNESS AS THE PREDISPOSING FACTOR IN PNEUMONIA AND IN THE COMMON COLD. A. LOCKE, J. Infect. Dis. **60**:106 (Jan.-Feb.) 1937.

Infections of the type encountered in pneumonia and in the common cold may result from slowing up of the mechanisms normally continuously employed in the removal of invading bacteria from the circulating blood. The slowing up may be body wide. It is manifested in the rabbit in a lengthening of the time required for recovery of a normal temperature after chilling and in man in a lengthening of the time required for replacement of oxygen after exercise.

The speed with which the temperature can be recovered in the rabbit and the speed with which oxygen can be replaced in man under defined conditions have been used to establish a rating of fitness, or an index of ability to support rapid performance of work. Ninety-two per cent of 12 rabbits with a rating of more than six tenths of the possible maximum survived intravenous infection with small numbers of virulent type I pneumococci without intermediate fever and without apparent injury. One hundred per cent of 11 rabbits with a rating of less than five tenths of the possible maximum died within three days after such infection. Sixty-nine per cent of 16 rabbits with the higher ratings gave negative blood cultures for more than twenty-six hours after the establishment of an intradermal focus of pneumococcic invasion. Forty-four per cent were carried through to recovery. Not one of 16 rabbits with the lower ratings was able to check invasion following intradermal infection or to survive.

Sixty-four per cent of a mixed group of 28 persons with ratings above six tenths of the maximum reported one cold or less between Oct. 1, 1935, and May 1, 1936. Eighty per cent of an equivalent group of 15 persons with ratings below five tenths reported four colds or more for the same period.

Influences which tended to lower or improve the rating in the rabbit were followed by parallel decreases in ability to survive pneumococcic infection. Among the factors which impaired fitness were: maintenance in overheated quarters, morphine poisoning, toxemia and starvation when accompanied with losses in weight in excess of 2.5 per cent per day. Among the factors which improved fitness were: removal to markedly cooler quarters, subcutaneous injections of from 0.1 to 0.4 cc. of anterior pituitary extract, intravenous injections of 1 cc. of an extract of adrenal cortex, intravenous injections of 2 cc. of a 20 per cent solution of an extract of liver and feedings of the same extract in consecutive daily doses of 20 cc.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

HAEMOLYTIC STREPTOCOCCAL MENINGITIS TREATED WITH PRONTOSIL: RECOVERY. C. F. LUCAS, Brit. M. J. **1**:557 (March 13) 1937.

Acute meningitis developed in a boy aged 9 years who had a discharging ear. Beta hemolytic streptococci were grown in pure culture from the spinal fluid. Two tablets of a derivative of sulfanilamide known as prontosil (the hydrochloride of 4-sulfamido-2′, 4′-diaminoazobenzene) were given by mouth three times a day, and 10 cc. of the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxy-naphthalene-3′, 6′-disulfonic acid was injected intramuscularly each day. The patient's temperature became normal at the end of thirty-six hours. The drug was administered for eight days. Recovery was complete.

ECHOLS, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

OBSERVATIONS ON SKIN SENSITIVITY IN ASTHMATIC AND CONTROL SUBJECTS. R. S. BRUCE PEARSON, Quart. J. Med. **6**:165 (April) 1937.

A comparative study of the cutaneous sensitivity of asthmatic persons and of normal controls was made. As a result of overlapping in the intensity of the reactions in the two groups, the author concludes that the value of cutaneous tests as a clinical procedure must be diminished and that no special importance can be attached to the presence of cutaneous sensitivity in individual cases unless its significance can be established on other grounds. As one might expect, the percentage of positive reactions and the proportion of large reactions were considerably greater among the asthmatic subjects, but positive reactions occurred with considerable frequency among the controls.

The review suggests that it would be significant if clinical asthma should later develop in some of the reacting controls.

BRADFORD, Rochester, N. Y. [AM. J. DIS. CHILD.]

DISTURBANCES IN TASTE AND SMELL AS LOCALIZING SIGNS IN LESIONS OF THE TEMPORAL LOBE. R. BRUN, J. belge de neurol. et de psychiat. **37**:262 (April) 1937.

Brun reports 2 cases of tumor of the temporal lobe associated with olfactory and gustatory hallucinations. Anosmia and hyposmia are not found in connection with central or cortical lesions of the olfactory or gustatory centers and consequently are of no diagnostic significance in localization of lesions of the temporal lobe. Perversions and hallucinations of smell and taste occur early and are of definite significance in the diagnosis of lesions of the basal and medial portions of the temporal lobe (hippocampus, uncinate gyrus and amygdaloid nucleus).

WAGGONER, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

OSTEOCLASTIC TUMOR OF THE PETROUS BONE. J. A. RAMADIER and A. TOURNAY, Rev. d'oto-neuro-opht. **15**:29 (Jan.) 1937.

The case reported is interesting because of the rarity of the condition and the surgical steps which led to the correct diagnosis and the use of roentgen therapy. Osteoclastic tumor, wrongly classed among the sarcomas, is not truly malignant, since it shows no tendency to recur or to form metastases. No case in which there was localization in the petrous bone has previously been recorded. A woman aged 36 suffered from an illness which began in August 1933 with neuralgic pains in the right hemicranium, radiating to the neck and the shoulder. Vertigo, tinnitus and deafness in the right ear next appeared, followed by peripheral paralysis of the facial nerve on the right side and, later, vomiting. The pains ameliorated in the morning and were increasingly severe later in the day, the severity lessening during the night. Lumbar puncture caused almost complete disappearance of the neuralgia. Examination revealed complete cochleovestibular paralysis of the right ear and a normal-appearing tympanic membrane. The results of a neurologic examination were normal, except for the seventh and the eighth nerve. There were no signs of cerebellar disturbance. The Wassermann reaction of the blood and of the spinal fluid were negative. A diagnosis of tumor of the cerebellopontile angle was made, and the region was exposed. No tumor or evidence of arachnoiditis was discovered, but an area of softening of the posterior wall of the petrous pyramid, near the internal auditory meatus, was observed. A second operation, two months later, disclosed a spot of softening in the anterior part of the attic, which was curetted, and a mass containing the superior semicircular canal was removed. Exploration of the anterior face of the petrous bone revealed normal dura and osseous cortex. A course of roentgen therapy resulted in apparent cure of the disease.

Two series of roentgenograms were made. The first, made before operation, showed destruction of the inner half or two thirds of the petrous bone; the second, made after the operations, revealed repair by excessive recalcification.

DENNIS, San Diego, Calif. [ARCH. NEUROL. & PSYCHIAT.]

VESTIBULAR DISTURBANCES OF CENTRAL ORIGIN: CROSSED AREFLEXIA AND TYPICAL VESTIBULAR DISHARMONY. J. A. BARRÉ and J. P. KIRCHER, Rev. d'oto-neuro-opht. **15**:241 (April) 1937.

Barré and Kircher suggest the term *hémiavestibulie latérale homonyme* to designate their syndrome of vestibular disharmony. A man aged 43 was wounded in the left occipital region during the World War. Headaches and disturbance in equilibrium soon appeared and increased in severity during the succeeding years. Examination revealed diplopia, disturbance of associated movements of the eyes and limitation of ocular movement and nystagmus to the left. There was deviation of the extended arms to the left. Caloric tests with water at 27 and at 44 C. gave correct reactions, but the threshold varied. In the right ear reaction occurred with the use of 40 cc. of cold water; with warm water the threshold was obtained only after the use of 200 cc. In the left ear the thresholds were

100 and 40 cc., respectively. The threshold with the galvanic current was at 1.2 milliamperes in the right ear and at 3 milliamperes in the left. A few signs of cerebellar disturbance were elicited, more marked on the left side. The patient's condition improved, and he returned home. He was admitted to the hospital three years later, complaining of severe headaches, change in disposition, vertigo, diplopia, intermittent vomiting and stiffness of the neck. Cerebellar tests gave slightly incorrect reactions on the left side. Spontaneous nystagmus and deviation of the left arm to the left were present. The threshold of reaction to cold water was obtained with 125 cc. in the left ear and with 300 cc. in the right ear. The headaches grew worse, and paresis of the palate, vomiting, bradycardia and slow respiration followed. The eyegrounds were normal. Exploration of the posterior fossa revealed three small encapsulated abscesses and a deeper, larger abscess with thin walls in the cerebellum. After recovery from operation the clinical vestibular signs were nystagmus, deviation of the left arm to the left and falling to the right in the Romberg test. In the caloric tests there was marked inequality of the threshold for the two ears. There were hyperreflexia of the vestibular fibers which cause nystagmus to the left and hyporeflexia of those which cause nystagmus to the right. This case demonstrates that it is possible to isolate two groups of vestibular symptoms, each with its own cause and evolution. The subjective symptoms of hypertension disappeared after the operation, and the signs of damage to the vestibular system persisted. The original injury caused, first, damage to the vestibular and cerebellar pathways in the brain, probably from small hemorrhages, and second, a group of late disturbances, attributable to a minimal, but persistent, infection, culminating in formation of abscesses.

DENNIS, San Diego, Calif. [ARCH. NEUROL. & PSYCHIAT.]

OSTEOPLASTIC AND OSTEOCLASTIC CARCINOSIS OF THE PETROUS BONE AND ITS MORPHOLOGIC RELATIONS TO OTOSCLEROTIC DEGENERATION OF THE BONE. A. GREIFENSTEIN, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **142**:231, 1936.

Greifenstein thinks that the rarity of reports on metastatic carcinoma in the petrous bone justifies him in describing typical osteoplastic carcinosis and osteoclastic squamous cell epithelioma. The bony labyrinthine capsule probably always remains free from true metastatic involvement and for a surprisingly long time remains free from the secondary spreading of the carcinoma. The development of an osteoplastic carcinoma in the petrosa is followed by lively processes of rebuilding, some stages of which may have a histologic similarity to otosclerotic changes. If these circumscribed carcinomatous processes of transformation come into topographic relation to otosclerotic foci, an exact delimitation may become impossible under certain conditions, the more so since there is histologic correspondence regarding the medullary fibrosis, the formation of blue reticular bone and the rarity of osteoclastic giant cells. Otosclerotic blue coverings are subject to the carcinomatous processes of rebuilding in the same manner as are the bones of the labyrinthine capsule. In the surroundings of a secondary and metastatic squamous cell epithelioma of the petrous bone, active rebuilding of the bone takes place, presenting the histologic aspects of osteodystrophia fibrosa and corresponding completely to certain manifestations of otosclerosis. In both types of carcinoma, the formation of primitive reticulated bone, which is rich in cement, is demonstrable; it corresponds to the so-called blue bone in young foci of otosclerosis. The pictures of the so-called sievelike perforation usually prove to be the early stages of this special form of the new formation of bone. EDITOR'S ABSTRACT.

DANGERS OF PARAVERTEBRAL ANESTHESIA OF CERVICAL PLEXUS: EXPERIMENTS ON CADAVERS. P. FALK, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **142**:254, 1936.

Falk points out that threatening complications and even sudden deaths follow paravertebral anesthesia. Experiments on cadavers proved that besides the possibility of direct injection into the lumbar sac or even into the spinal medulla, the

anesthetic substance may reach the dural sac and the spinal medulla by way of the nerve sheath in case of endoneural injection into a branch of the cervical plexus or into the cervical ganglion. In a case of paravertebral anesthesia of the cervical plexus which the author observed death resulted from injection into a branch of the cervical plexus and passage of the anesthetic fluid through the nerve sheath into the lumbar sac and the posterior crescent of the spinal cord, where a traumatic hemorrhage resulted. The author thinks that paravertebral anesthesia, according to Kappis, to Braun and to Härtel, should be avoided on account of the danger involved. The method of Kulenkampff, although without danger, often fails to produce adequate anesthesia. The method of Soerensen was used by the author successfully in more than 100 cases, but then suddenly it caused a fatality. Nevertheless, he thinks the last method permissible, with the restriction that it is inadvisable to inject more fluid while the needle is withdrawn from the depot position, for this involves the danger of endoneural injection.

EDITOR'S ABSTRACT.

VERTIGO IN DISEASES OF BRAIN STEM. R. LEIDLER, Monatschr. f. Ohrenh. **70**: 1315 (Nov.) 1936.

According to Leidler, lesions of the brain stem frequently involve the central vestibular system. It is known that these disorders are often combined with vertigo, but nothing definite is as yet known regarding the localizing function of vertigo. The author shows that the investigation of vertigo is not identical with that of the vestibular reflexes and their disturbances, in spite of the fact that they have to go together. Manifestations on the part of the sympathetic system are important in recognizing the symptoms of vertigo, but here again are unsolved problems: 1. When are the sympathetic disturbances that accompany vertigo caused by the connections of the vestibular system with the sympathetic center in the medulla oblongata and when by the connections with the higher sympathetic centers in the diencephalon? 2. How in various types of encephalitis does the disorder produce spontaneous vertigo on one side and remain refractory to vertigo-eliciting stimuli of the labyrinth on the other side? 3. What is the role of the thalamus in the pathogenesis of vertigo? In conclusion the author emphasizes that vertigo can be regarded as a symptom neither of irritation nor of inhibition, for it is always both and is the psychic correlative for the disturbances in the regular course of all those mechanisms which insure the unconscious function of the labyrinth.

EDITOR'S ABSTRACT.

SPONDYLITIS CAUSED BY SAFETY PIN IN ESOPHAGUS. H. NAVIS, Ztschr. f. Hals-, Nasen- u. Ohrenh. **41**:159, 1936.

After reviewing the literature on safety pins in the esophagus, Navis reports an unusual case that was observed at the clinic in Leyden, Netherlands. A boy aged 3 was referred to the otorhinolaryngologic clinic by the orthopedic clinic, to which his parents had brought him on account of an extremely curved back. The roentgenogram of the vertebral column revealed an open safety pin apparently in the esophagus, approximately at the bifurcation, at the level of the fifth and the sixth thoracic vertebra. These two vertebrae showed a spondylitic process and the question arose whether this process had a connection with the presence of the safety pin. Already at the age of 18 months the child had been examined at the orthopedic clinic, because sitting up was difficult. At that time the vertebrae showed no lesions, but the safety pin was in the same position. However, no attention was given to it, because it was probably assumed that the pin, like several buttons which appeared in the roentgenogram, was in the clothing. In order to determine whether the spondylitis was caused by the safety pin, a new roentgeno-

gram was made after contrast medium had been introduced into the esophagus. The pointed part of the needle was behind the esophagus. It is assumed that the spondylitis had been caused by the inflammation, which, in turn, had been elicited by the perforation of the safety pin. It is peculiar that, with the exception of the curved back, the parents never noticed anything unusual. The child had always been able to eat everything and had never complained of pain. When told of the presence of the pin, the parents recalled that recently the child had not eaten properly and had repeatedly cried "pinprick." The pin was removed by esophagoscopic technic.

EDITOR'S ABSTRACT.

Society Transactions

AMERICAN OTOLOGICAL SOCIETY

HARRIS P. MOSHER, M.D., *President, Presiding*

Seventy-First Annual Meeting, Atlantic City, N. J., May 5-6, 1938

ABSTRACTED BY DR. ALFRED LEWY, CHICAGO

Thursday Morning Session, May 5

ADDRESS OF PRESIDENT: THE RESULTS OF THE EXPERIMENTAL FEEDING AND INJECTING OF QUININE ON THE MIDDLE AND INTERNAL EAR OF THE GUINEA PIG. DR. HARRIS P. MOSHER, Boston.

Small hemorrhages are commonly found in the basal whorl in the scala tympani. Four or five control animals showed this condition. Hemorrhage in connection with the administration of a drug, can be laid to the drug only when the blood vessels of the cochlea are congested. When there is extensive hemorrhage in the cochlea, serial sections show that it often overlies a blood vessel. This explanation is more satisfactory than the commonly held belief that the blood reaches the cochlea from the cranial cavity and is an artefact.

The cochlear aqueduct is filled with a fine network of fibrous tissue and acts as a sieve. When there is much blood in the basal whorl of the cochlea, corpuscles in diminishing amounts are found toward the cranial end.

An experimental animal killed by two blows on the side of the head without fracturing the skull was found to have abundant hemorrhage in the cochlea. In order to check the theory that hemorrhages may be due to suffocation attending anesthesia induced by chloroform, a pig was slowly strangled to death after primary anesthesia with ether; it showed no hemorrhages in fifty serial sections of the cochlea.

My experiments on animals showed that quinine, sodium salicylate and mapharsen, fed to the mother or injected, caused hemorrhages in the cochlea of the fetus. Mapharsen produced the most extensive hemorrhages, but the cochlea of the mother of the pig showed no hemorrhages. Hemorrhages in the fetus were in the scala vestibuli, the vestibule and the semicircular canals and were extensive. In the animals which received quinine and sodium salicylate the hemorrhages were also in the scala tympani. The findings seem to indicate that quinine and mapharsen have a selective action on different parts of the inner ear. The favorite sites for hemorrhage into the mesenchymal tissue of the ear are surrounding the ossicles, in the tissue covering the cochlea at its base and in the tissue lining the cavity of the bulla.

Drugs sometimes pass from the mother to the fetus, as shown by similar findings in both. What happens in animals probably also happens in man.

SYMPOSIUM: WHAT TREATMENT FOR OTITIC MENINGITIS IS JUSTIFIABLE?

(*a*) A HISTORICAL REVIEW OF THE SURGERY OF OTITIC MENINGITIS. DR. THOMAS J. HARRIS, New York.

The historical review serves as a brief introduction to the symposium on otitic meningitis. It gives a summary of the surgical procedures that have been under-

taken for the relief of the condition which covers seventy-five years. The procedures are chiefly three:

1. Ventricular puncture and drainage.
2. Drainage of the spinal subarachnoid space.
3. The introduction of drugs into the subarachnoid space.

All these, carried out by the best surgeons in the world, resulted in failure but served as an introduction to the most recent form of treatment, the administration of sulfanilamide, which has resulted in astounding cures.

DISCUSSION

Dr. John J. Shea, Memphis, Tenn.: Surgical treatment of otitic meningitis has two objects: (1) external drainage for the infected area, and (2) drainage of the subarachnoid spaces, (*a*) for elimination of septic material, (*b*) to relieve intracranial pressure and (*c*) to accelerate the production of cerebrospinal fluid for irrigation of the subarachnoid spaces and replacement of fluid lost by drainage.

The decision to operate depends on the following factors: 1. The condition of the patient must permit surgical intervention. 2. Roentgenologic evidence of destruction of bone should indicate the possibility of direct extension. Local anesthesia induced by a basal anesthetic is preferable, and operation should be limited to the provision of continuous free external drainage. If meningitis is suspected lumbar puncture should precede operation. Diagnosis depends on the culture. When a meningococcus is present, antimeningococcus serum and sulfanilamide are required, but there is no need for continuous drainage. A pneumococcus should be typed and suitable serum administered. Continuous drainage seems useless for pneumococcic meningitis but should be instituted for staphylococcic or streptococcic infection.

An indwelling needle will accomplish adequate drainage, laminectomy thus being avoided. The fluid balance must be maintained. Concentrated dextrose solution dehydrates the brain. In order to maintain sodium ions in the circulation, physiologic solution of sodium chloride or blood transfusions are best for intravenous administration. Dextrose in 5 per cent solution is administered for the maintenance of caloric requirements. Forcing of fluids by mouth is indicated. Sulfanilamide is more successful against the streptococcus than against other bacteria. A saturation of the blood, of 10 to 15 mg. per hundred cubic centimeters, should be maintained. This requires administration of 0.1 to 0.2 Gm. per kilogram of body weight every twenty-four hours. Infants and younger children require perhaps a 50 per cent increase in the dose. Cyanosis may be controlled by administration of methylthionine chloride, 1 unit to each 10 units of sulfanilamide by weight.

(*b*) Indications for Surgical Treatment of Suppurative Meningitis. Dr. James G. Dwyer, New York.

Surgical treatment of meningitis is directed to the focus if it can be established. There must be some clew to the pathway and a thorough knowledge of the pathologic and the bacteriologic picture. Surgical intervention is not advisable in all cases. In some it is useless or contraindicated.

The clinical symptoms are familiar, but the final diagnosis depends on the findings in the spinal fluid. Another important aid is the examination of the blood.

Examination of the Spinal Fluid.—The examination should be (1) physical, (2) chemical, (3) cytologic, (4) serologic and (5) bacteriologic.

Two tubes of spinal fluid and one of blood are taken and sealed with freshly melted paraffin.

Normal spinal fluid is clear and exudes dropwise without force. Pathologic fluid may be clear to thick and cloudy. It may be blood stained if a vessel is injured. Cloudy fluid indicates a pathologic process, but a distinction must be

made between organisms present and organisms absent. Cloudy fluid is the result of the reaction of the tissue. If the infection is extradural there are no organisms in the fluid. If the infection has broken through, organisms are present, usually accompanied by diffuse suppurative meningitis. An analogous situation is seen in cases of hypopyon. If the infection has not broken through the cornea, the purulent fluid in the anterior chamber is sterile.

The recognition that sterile cloudy fluid means extradural infection is a strong indication for surgical removal of the focus. In cases of this type, the results are satisfactory.

Chemically, pathologic fluid shows increase in lactic acid and globulin, and the sugar-reducing substance often disappears.

Cytologically, 3 to 5 cells per cubic millimeter are present; usually the lymphocytes are normal. Clear fluid with increased numbers of lymphocytes is usually syphilitic or tuberculous.

The serologic examination should include classification of pneumococci. A streptococcus may be tested against various antistreptococcus serums.

In making the bacteriologic examination one should remember that much confusion has resulted from failure to report the presence or absence of bacteria and whether they are found in the smear alone or in the culture. The meningococcus is gram-negative; all other cocci in spinal fluid are gram-positive. Gram-positive cocci when degenerating may become gram-negative. One to 2 cc. of centrifuged fluid should be planted to insure growth.

In cases of suppurative meningitis the white cell count is usually high, as is the percentage of polymorphonuclears.

Types.—The types are acute, subacute and chronic.

The term acute designates the fulminating type, such as follows dislocation of the stapes, direct injury to the meninges or sudden invasion before any protective wall is built up. Surgical intervention is probably of no avail. The chronic condition is only relatively so. Ambulatory patients, with only a slight fever and headache, may suddenly become violently ill after weeks. This condition is often due to the type III pneumococcus.

In most cases the condition is subacute and lasts a week or ten days. This is the type of case in which skill and judgment may lead to a successful result.

Pathologic Picture and Pathways of Infection.—The primary reaction is a protective one. Extension is in the form of osteitis, periostitis or osteomyelitis, and the pathologic picture is that of thrombophlebitis. The condition may arise also by direct extension, by injury or by infection of the blood stream. The pathway is usually through the mastoid cells but may be through the lymphoid tissue of the nasopharynx or from the nasal accessory sinuses. There are small areas of medullary matter in the temporal and other bones at the base of the skull, and one must be careful in the diagnosis of the pathway of infection. Some believe that infection occurs only through the cells of pneumatic bone; others, that it may appear at distant points by thrombophlebitic extension and that, for instance, an otologic infection may result from a sphenoid infection by thrombophlebitic extension.

(*c*) Otitic Meningitis from the Surgical Standpoint. Dr. Isidore Friesner, New York.

The various forms of meningitis as differentiated by laboratory examinations, particularly in the presence of analogous clinical phenomena, are all due to an infectious process within the meninges, and all the differences are merely of degree and extent.

Any operation designed for the cure of meningitis which has as its sole purpose the drainage of the cerebrospinal fluid, no matter how this is accomplished, must of necessity fail of its objective. Extension of infection in the meninges does not take place solely by diffusion, but infection probably does spread along the vessels.

The point of view of many, that the condition should be classified as healed suppurative meningitis only in those cases in which organisms have been demonstrated in the spinal fluid, is at variance with the opinions of others, who regard the presence of few cells in the spinal fluid as abnormal and the increase to more than 5 cells per cubic millimeter as significant of an early stage of meningitis. This apparently extreme difference of opinion as to what constitutes meningitis is understandable. It is evident that some change in attitude must obtain in order that the therapy of meningitis and its indication be clarified.

Changes in the spinal fluid, whether they are only an increase in the cell content or the presence of viable bacteria, are to my mind expressions of the degree, severity and extent of the inflammation in the meninges. I feel that as soon as these changes in the spinal fluid are discovered the indication for eradication of the suppurative focus is established, and in the last analysis the surgical treatment of meningitis is the early and complete eradication of the focus from which the meningitis takes its origin.

DISCUSSION

Dr. Wells P. Eagleton, Newark, N. J.: Removal of the focus of infection is fundamental. Although a successful remedial treatment is instituted, failure to remove the focus may ultimately result in death.

The factors favoring recovery are limitation of the focus of infection in the bone and the presence of protective meningitis.

When there are few or no bacteria in the spinal fluid, as mentioned by Dr. Dwyer, the mortality should not exceed 5 per cent.

The usual types of meningitis are:

1. Infection at the angle of the petrosal sinus. The lateral arm of the basal cistern is filled with infected fluid.

2. Infection of the saccus endolymphaticus from adjacent osteomyelitis or from retrograde thrombophlebitis from the jugular bulb. An unlocking operation exposing the saccus, if done before general leptomeningitis ensues, is usually successful.

3. Infection within the internal auditory meatus from the labyrinth. The labyrinth should be drained through the middle ear and the arachnoid prolongation surrounding the meatus (cisterna pontis lateralis?) incised.

4. An old suppuration in the labyrinth. The pyramid should be unlocked and the lateral sinus freed and retracted as far as the adhesion of the dura to the lip of the internal auditory meatus.

5. Infection from the petrous apex. This causes 50 per cent of all intracranial complications from the ear. The apex should be fully unlocked and exposed before the dura is opened.

6. Meningitis involving the jugular bulb, with infection of the fluid in the lateral cistern. Evacuation of the fluid and removal of the surrounding medullary bone are necessary, to get rid of the infected small veins. Subsequent infection is avoided by immediate closure of the dural opening with a graft of mucosa from the lip. Fascia lata is not actively proliferating and dies early.

7. Toxic and allergic types of nonsurgical meningitis and scarlatinal streptococcic and pneumococcic meningitis, with a concomitant suppurating ear. The latter is to be treated surgically, but the meningitis should be regarded from the point of view of the causative scarlet fever or pneumonia. The overflow of bacteria is attenuated, and the condition does not require drainage of the cerebrospinal fluid.

(*d*) Treatment with Sulfanilamide. Dr. Emanuel Appelbaum, New York.

The object of this paper is to present mainly the experience of the Meningitis Division of the New York Health Department with sulfanilamide in the treatment of meningitis secondary to infections of the ears and sinuses.

Sulfanilamide and its various derivatives have been used too short a time to admit of definite conclusions in regard to the relative merit of the different compounds, the best routes of administration and the dosage. The preparations that have been used are sulfanilamide orally, prontosil (disodium-4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate; now known as neoprontosil) intramuscularly and at times an 0.8 per cent solution of sulfanilamide intraspinally, subcutaneously or intravenously. Recently my associates and I have used also prontosil in solution intraspinally and in powder form orally. As a rule, 5 cc. or less of the prontosil solution has been given every four hours to younger children and 10 cc. every four hours to older children and adults. In addition, from 5 to 15 grains (0.32 to 0.97 Gm.) of sulfanilamide has been given every four to six hours. The same dosage was followed when prontosil was given by mouth. We do not feel sure at present that there is any advantage in administering sulfanilamide intraspinally.

While sulfanilamide is a therapeutic agent of great value it has also toxic qualities, the most serious of which is the production of hemolytic anemia and of granulocytopenia. We have not encountered any of the more serious reactions. We do not consider cyanosis an indication to stop the drug.

We have used sulfanilamide in the treatment of 5 miscellaneous infections of otitic or sinal origin, with 4 recoveries and 1 death.

A patient with meningitis due to Bacillus influenzae treated with this drug died.

There were 3 cases of meningitis due to the nonhemolytic streptococcus, with 1 recovery.

We have used sulfanilamide in 32 cases of pneumococcic meningitis. In most of these, the condition was associated with otitis or infection of the sinuses or of the upper part of the respiratory tract; occasionally it followed pneumonia. In this series there were only 4 recoveries. While the clinical results from the treatment of pneumococcic meningitis with sulfanilamide are far from satisfactory, they are nevertheless encouraging.

The use of sulfanilamide in cases of hemolytic streptococcic meningitis has yielded astounding results. We have had 26 cases, with 21 recoveries and 5 deaths.

It is important in treating all forms of meningitis adequately to drain the subarachnoid space. The prompt and complete eradication of the primary foci of infection is of particular importance when meningitis is secondary to infection of an ear or a sinus.

DISCUSSION

Dr. Josephine B. Neal, New York: I have always questioned the efficacy of sulfanilamide against infections in bony tissues, as I have often seen persistence of the infection in spite of adequate dosage and in spite of the fact that the course of the disease was evidently prolonged.

I recall 1 patient who did not recover entirely after a mastoidectomy until the other mastoid was operated on. This occurrence emphasizes the need of early diagnosis and removal of all foci of infection.

When block occurs in infants with open fontanels ventricular is preferred to cisternal puncture. It is safe and more likely to be effective. No fatalities have followed cisternal puncture in over 30 cases. It is more dangerous in the presence of adhesions and congestion of the blood vessels, as in cases of meningitis, than in cases of syphilis.

"Forced drainage" has been tried without any favorable effect. In some cases unfavorable effects appeared at necropsy. The results of sulfanilamide in the treatment of hemolytic streptococcic meningitis have been amazing. There were a few deaths, mostly due to attendant circumstances, but what medication gives 100 per cent recoveries?

I repeat Dr. Applebaum's praise of sulfanilamide and point out that reliable products must be used.

In conclusion I should like to challenge the members of the society to find methods for earlier diagnosis of mastoiditis and sinusitis.

DR. PHILIP E. MELTZER, Boston: Drs. Dwyer, Friesner and Eagleton emphasized removing the focus. Is it always possible to find it definitely in the absence of a pathway of necrotic bone or at least an inflammatory reaction of convincing degree?

In the cases in which one cannot tell, what procedure is advocated? How far is the decompression of the cerebral fossae carried? Are removal of the entire anterior surface and exposure of the carotid canal advocated? What is done about the posterior surface and the group of cells underlying it?

DR. MOSES H. LURIE, Boston: Has the New York Health Department been doing blood tests for immunity on patients treated with sulfanilamide? Dr. Lyons, at the Massachusetts General Hospital, has and finds that when systemic resistance is poor the sulfanilamide does not act so well. After transfusion from an immune donor the sulfanilamide was found to increase from three hundred to five hundred times the patient's ability to absorb and destroy the infective organisms.

DR. BURT R. SHURLY, Detroit: Perhaps after an experience of forty years one is entitled to grow first enthusiastic and then displeased. It is of greatest value to recognize one of the splendid discoveries of the last few years. Sulfanilamide, in my experience, is one of the greatest things known to therapeutists for the treatment of infections of the nose, throat and respiratory tract extending down to the lungs. Of the last 100 patients with pneumonia treated in the hospital with which I am associated, 6 have died. My colleagues and I used diathermy twice a day and the highest possible dosage of sulfanilamide. The dangers of the use of this drug must be recognized by the profession. Druggists are selling it over the counters as they sell acetylsalicylic acid. There are toxic symptoms that can be determined only by daily examination of the blood. We had 4 patients with mastoiditis and 1 with petrositis prepared for operation in accordance with the opinion of several surgeons. They were placed under observation in the hospital for twenty-four hours, with oral and hypodermic administrations of sulfanilamide. The improvement was so great that the treatment was continued, and the patients have recovered without surgical intervention. It is only under observation in a hospital that one can afford to allow operation to be delayed, because the best surgical judgment followed by removal of the focus is necessary.

The toxic symptoms, cyanosis and acidosis, can be relieved by the use of 30 Gm. of bicarbonate of soda with the sulfanilamide. Patients with toxic conditions which result in acute hemolytic anemia or optic neuritis in the presence of renal insufficiency and those that are in a bad general toxic condition should be watched with even greater care. The table for dosage should definitely be given out to the members of the medical profession (e. g., 160 pounds [72.6 Kg.], first dose 120 grains [7.76 Gm.]), but dosage should be determined by the study of the individual case. We feel this medication should be continued through the night. We gave the dosage six times during twenty-four hours. One cannot expect the same results in cases in which Streptococcus haemolyticus is not the infecting organism, although we have had improvement of great value in cases of pneumococcic infection.

DR. BERNARD J. MCMAHON, St. Louis: My associates and I have conducted experiments on rabbits with the idea of determining the amount of sulfanilamide deposited in the tissues of the nose and sinuses. Dr. Arellano has mentioned that sulfanilamide is not deposited in bone. The sinal walls are not solid bone, but a thin type of bone, transversed by many openings and filled with areolar tissue and with capillaries which have a relatively large amount of mucosal covering.

Dr. Neal mentioned that she had seen no good results from treatment of sinal infections with sulfanilamide. I believe these are mixed infections. We found in the blood of our rabbits sulfanilamide, from 17 to 75 mg. per hundred cubic centimeters, and in the nasal tissues from 17 to 47 mg. per hundred grams. Marshall, Emmerson and Cutting found 19 mg. per hundred grams in the liver, as a maximum, and 3 mg. in fat, as a minimum, when the hemolytic streptococcus was

established in the sinuses of rabbits. Sulfanilamide was then given four consecutive days in maximum doses, and the rabbit was killed. We did not attempt to cure the sinal infection entirely, because we were interested in determining the effect of sulfanilamide when infection was present in the tissues. No considerable pathologic changes resulted from the administration of sulfanilamide, with or without infection. Those which were present were due to the infection. The administration of the sulfanilamide did not influence the number of polymorphonuclears or monocytes or the amount of phagocytosis. The toxic signs are important. One of the toxic signs in our rabbits was hyperpnea, coming on as early as eighteen hours after as small a dose as 1.5 Gm. per kilogram. In other rabbits, with five times this dose, there were no toxic signs. However, in the majority of our rabbits toxic signs did develop. Hyperpnea usually occurred first, then apathy and later spastic and flaccid paralysis, especially of the hindlegs. The toxic signs usually abated in the reverse order of their onset.

We feel confident that sulfanilamide is deposited in the nasal and sinal tissues, and if the infective agent is a pure streptococcus one can be reasonably assured that it will be effective, as it is against streptococcic infection elsewhere. We believe this applies also to the mastoid, although we made no actual examinations of tissue of infected mastoids.

Dr. James G. Dwyer, New York: I emphasized in the beginning that if one could find the focus common sense must guide in one's procedure. In many cases, by study one can get an indication of the source of infection. At postmortem examination masses of thrombosed vessels from the bone into the dura have been found. In such cases, if one removes the bone and removes the infection one will accomplish a great deal. As Dr. Shurly pointed out, several patients that were prepared for operation got well without it.

In the report to be made tomorrow is a description of 3 cases of meningitis with complications in the mastoid in which patients refusing operation recovered. That is not advocated. The value of removing the focus can be overstressed. If there is one and it is accessible, it should be removed.

Dr. Emanuel Applebaum, New York: The question of eradication of the primary foci is a surgical one, which I am not qualified to answer. It is to be noted that 8 of 26 patients recovered without operation. Perhaps a more effective agent will be found which will make it unnecessary to operate on the primary foci.

My associates and I have made no studies of immune properties in the patients' serum during recovery. Antiscarlatinal serum or serum from patients convalescent from scarlet fever has not been successful against streptococcic meningitis. Recent work by Branham and Rosenthal indicates that a combination of specific serum and sulfanilamide yields better results than either agent alone in the treatment of meningococcic and pneumococcic infections in mice. It is our clinical impression that this is true of meningococcic meningitis.

Surgical Technic for Conservation of the Hearing in Cases of Chronic Mastoiditis. Dr. J. M. Smith, New York.

The operations for chronic mastoiditis are classified, according to the anatomic and pathologic conditions present, into four classes: (1) the complete simple operation, (2) the complete simple operation plus the removal of the incus, (3) the new radical operation and (4) the complete radical operation.

The complete simple operation is the usual antrotomy, with wide exposure of the antrum and dissection of the root of the zygoma until the short process of the incus is thoroughly exposed. All accessible granulation tissue in the posterior part of the aditus is removed. Hydrogen peroxide and saline solution are used to flush the cavity during operation. A cigaret drain is inserted into the antrum, and plastic repair is not done on the canal. This operation is chiefly indicated for the treatment of young children and the conservation of hearing.

The complete simple operation plus removal of the incus is performed like the one just described. The incus is dislocated backward into the antrum by a eustachian curet and removed. The malleus is now visible but is not disturbed. All accessible granulations are carefully removed. The removal of the incus has little effect on the hearing. Postoperative care is like that for the foregoing operation. Plastic repair is not done.

The new radical operation is the same as the two just described, but a small part of the bridge next to the incus is removed from within outward to enlarge the aditus. The eustachian curet is used to dislodge the malleus and is removed with a small forceps. This enlarges the space connecting the mastoid cavity and the external auditory canal and permits through and through irrigation. The membranous canal is not disturbed. Through a speculum in the external canal, granulations may be curetted from the promontory downward, backward and forward, with avoidance of the facial nerve and stapes. Remnants of the drum membrane may be removed. The annulus is allowed to remain. The eustachian tube is curetted. After irrigation, alcohol is freely used. A folded rubber tissue is inserted into the opening between the middle ear and the mastoid antrum. A cigaret drain is inserted into the canal and middle ear and another into the antrum. Daily through and through irrigations are essential. The objective is a dry, clean middle ear with a healed mastoid wound.

The complete radical operation is chiefly indicated after failure of one of the procedures just described or when the internal ear is involved or there is intracranial extension, paralysis of the facial nerve, petrositis or extensive cholesteatoma.

A series of case reports illustrates the opinions expressed.

The technic described not only conserves but improves the hearing in many instances.

DISCUSSION

Dr. H. I. Lillie, Rochester, Minn.: Cases of chronic suppurative otitis media in which a cure has been effected by natural reparative processes have been generally observed. All the surgeon can do is to help these processes accomplish their aim by removing the obstacles. The recognition of these obstacles is surgical judgment.

For the choice of the technical procedure for combating a given pathologic process, the history often may give more important information than the examination. I feel that when the presence of cholesteatoma is strongly suspected, some form of radical operation must be used. I am in close agreement with Dr. Smith about operative measures through the external auditory canal. Pathologic processes in which the posterior and the superior bony wall of the external auditory canal have been destroyed by the disease, only the membranous canal being left, have been observed. The intra-aural removal of the overlying membranous meatus and postoperative treatment were sufficient to effect a cure. If the bony wall has not been destroyed no intra-aural surgical measure will be adequate.

If the pathologic lesion is such that life is threatened, the conservation of hearing is secondary. A prosthesis can be used.

Patients are disappointed with results of operation on the mastoid if the discharge persists. If the disease is situated in the attic and mastoid antrum and if the drum and ossicles are present and the defect is too small to permit direct treatment, the modified radical operation is to be preferred. It helps conserve the hearing, does not expose normal membranes on the promontory and in the eustachian orifice and thus prevents a discharging ear. Unless the promontory is covered by scar tissue, the ear is always moist.

Dr. John R. Page, New York: It is good to hear Dr. Smith emphasize the obligation to develop different methods for different conditions of chronic mastoiditis and to preserve and improve hearing whenever it is possible to do so with safety to the patient. In 1925 an article on this subject was published from the clinic with which I am associated. It recommended preliminary removal of tonsils

and adenoids. It agreed with Dr. Smith that the type of operation should depend on the conditions found and on the degree of hearing present and that one ought not to follow the more radical procedure unless led to do so by a condition found in the mastoid. It recommended careful consideration of the hearing and of the condition of the ossicles before the removal of any of them, particularly when the hearing is good, as it is usually the disease around them rather than the disease of the ossicles themselves that is a menace.

Even with great destruction of the drum membrane, if safe for the patient the conservative mastoid operation or some modification of it to suit the individual case and time for ventilation and treatment through a wide meatus are recommended.

Opposition to lowering the posterior wall of the canal and constructing a new meatus is not quite clear. A large cavity in the mastoid can be avoided by removing the tip and the ridge over the digastric muscle. In many cases the cortex can be beveled back so that the soft parts fall in close to the inner plate. It seems that when the membranous and bony canal are left intact, narrower access to the part to be treated and poorer ventilation will be obtained. It seems that with removal of the incus alone the drum membrane acts more as an obstruction or baffle than as an aid to hearing and that it might better be removed like a false membrane that sometimes forms across the tympanic part of the cavity left by a radical mastoidectomy.

There has been a growing tendency at the clinic to attempt preservation of the drum and ossicles in cases in which the hearing is too poor and the tympanum too much involved to warrant it. The radical mastoidectomy is more apt to improve the hearing in such cases than is the modified operation. This tendency is probably due to the after-treatment, which is more painful and prolonged than that after the conservative operation.

Dr. Smith is to be congratulated on his good work. In his hands results are obtained through a narrow canal that in other hands are better obtained through a wide one.

DR. J. M. SMITH, New York: The decision to leave the wall of the canal is optional and must be made according to the operator's results. If cutting a flap is avoided one avoids a cavity as well as much after-treatment.

On account of the tendency of cholesteatoma to recur, I believe a complete radical operation is preferable if there is a normal ear on the other side.

CORRECTION

In the article by Dr. Samuel J. Kopetzky entitled "Purulent Otitis Media, Sinus Thrombosis and Suppuration of the Petrous Pyramid: Acute and Chronic Forms," which appeared in the October issue (ARCH. OTOLARYNG. **28**:626, 1938), the term "middle cranial fossa" at the end of the tenth line from the top of page 647 should have read "posterior cranial fossa."

Book Reviews

The Life of Chevalier Jackson: An Autobiography. By Chevalier Jackson, M.D. Price, $3.50. Pp. 229, with 80 illustrations. New York: The Macmillan Company, 1938.

One has a certain trepidation in approaching an autobiography, but this will be completely dispelled in the perusal of such a sincere and fascinating medical romance as this recorded life of Chevalier Jackson, the motive of which is to present, not a chronicle of achievement, but, in his own words, "a sugar coated pill on preventive medicine." The record of hardships in the brutal contacts of his sensitive childhood, in the almost insurmountable difficulties in obtaining an education and in service ranging from that of a plumber's cub to the cook's galley on the codfish banks finds perhaps a certain parallel in the thrilling path to scientific heights chronicled for Madame Curie by her daughter.

Early flashes which forecast the bronchoscope appear in this life history, such as the invention of the fishing tool to extract the sodden mass of cord in a broken-down oil drilling apparatus, the devising of a method for the extraction of the pushed-in cork of an olive bottle and the accumulation of experience with the varied types of valves essential to pipes, pumps and plumbing later to be applied to human bronchial tubes.

His expression that bronchoscopic work, so close to the beating heart, realizes the ideal of being close to the very machinery of life is perhaps characteristic of the man.

Coincident with the constant depression of his developmental period, bits of fine philosophy appear. The fundamental biologic fact that death is an irreversible process was deeply impressed while he struggled for the life of a little injured rabbit and remained as a constant fear lest his patients cross this irremeable line; the dogged determination to suffer in silence the abuse of childhood, with the apologetic acceptance of the school bully's attitude as a defense mechanism, fits the pattern of his later irresistible spirit. His patience in fighting repeated pulmonary crises, with an insatiable longing for health to complete his mission, accords with the generosity pervading his entire medical life.

One is impressed with an essential orderliness in routine, even in early life, and in his later indefatigable devotion to his life's work the careful education, really self education, in all that would contribute to a completely artistic culmination seemed almost an obsession. His positive views on the obligation of medical appointments and his specific principle in medical writing that there should be a clear separation of clinical facts from deductions and opinions are a logical sequence. The careful preservation of all the important correspondence which appears in this volume is but another evidence.

To these traits were added a cheerful omission of entangling social engagements, the preference for early morning literary work in solitude and total abstinence from alcohol and tobacco, for the sake of a clear head and a steady hand, as well as on moral principle. This teacher has been an artist of rare ability, has idealized womanhood, has had the gentlest touch with children, has been generous to a fault with assistants and has bestowed little thought on money.

This review should perhaps have been more critical, but one finds little to criticize, and I do not agree with one statement, that "it is not a doctor's book"—this stimulating narrative might be read with value before, during and after the medical education of every student.

Directory of Otolaryngologic Societies *

FOREIGN

COLLEGIUM OTO-RHINO-LARYNGOLOGICUM AMICITIÆ SACRUM

President: Dr. Louis Ledoux, Brussels, Belgium.
Secretary: Prof. Dr. C. E. Benjamins, Verlengde Heereweg 143, Groningen, Netherlands.
Place: Brussels, Belgium. Time: September 1939.

HUNGARIAN OTOLARYNGOLOGICAL SOCIETY

President: Dr. J. Treer, Bocskay-u. 9, Szeged.
Secretary: Dr. G. Kelemen, Reáltanoda-u. 9, Budapest.

SOCIEDAD RIOPLATENSE DE OTO-RHINO-LARINGOLOGÍA (ARGENTINE SECTION)

President: Dr. Raul Becco, B. Mitre 1690, Buenos Aires.
Secretary: Dr. Juan Manuel Tato, Santa Fé 1171, Buenos Aires.

SOCIÉTÉ FRANÇAISE D'OTO-RHINO-LARYNGOLOGIE

Secretary: Dr. Henri Flurin, 19 avenue Mac-Mahon, Paris (17°).
Time: Oct. 24-26, 1938.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY

Chairman: Dr. H. Marshall Taylor, 111 W. Adams St., Jacksonville, Fla.
Secretary: Dr. Leroy A. Schall, 270 Commonwealth Ave., Boston.
Place: St. Louis. Time: May 15-19, 1939.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George M. Coates, 1721 Pine St., Philadelphia.
Executive Secretary: Dr. William P. Wherry, 1500 Medical Arts Bldg., Omaha
Place: Chicago. Time: October 1939.

AMERICAN BRONCHOSCOPIC SOCIETY

President: Dr. John D. Kernan Jr., 120 E. 75th St., New York.
Secretary: Dr. Lyman Richards, 319 Longwood Ave., Boston.

AMERICAN LARYNGOLOGICAL ASSOCIATION

President: Dr. George B. Wood, 504 Physicians' Bldg., Philadelphia.
Secretary: Dr. James A. Babbitt, 1912 Spruce St., Philadelphia.

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

President: Dr. Harold I. Lillie, Mayo Clinic, Rochester, Minn.
Secretary: Dr. C. Stewart Nash, 708 Medical Arts Bldg., Rochester, N. Y.

SECTIONS:

Eastern.—Chairman: Dr. Frank E. Kittredge, Masonic Temple, Nashua, N. H.
Place: Boston. Time: Jan. 11, 1939.
Southern.—Chairman: Dr. Francis E. LeJeune, Maison Blanche Bldg., New Orleans.
Place: New Orleans. Time: Jan. 14, 1939.
Middle.—Chairman: Dr. T. R. Gittins, Davidson Bldg., Sioux City, Iowa.
Place: Sioux City, Iowa. Time: Jan. 19-20, 1939.
Western.—Chairman: Dr. Frederic G. Sprowl, Medical Arts Bldg., Spokane, Wash.
Place: Spokane, Wash. Time: Jan. 29, 1939.

AMERICAN OTOLOGICAL SOCIETY

President: Dr. Isidore Friesner, 36 E. 73d St., New York.
Secretary: Dr. Thomas J. Harris, 104 E. 40th St., New York.

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* Secretaries of societies are requested to furnish the information necessary to keep this list up to date.